moving from start (N-terminus or 5′) to end (C-terminus or 3′), such that for an alignment that extends to p monomers (where $p>x$) there are $p-x+1$ such windows, each window has at least $x \cdot y$ identical aligned monomers, where: x is slected from 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200; y is selected from 0.50, 0.60, 0.70, 0.75, 0.80, 0.85, 0.90, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99; and if $x \cdot y$ is not an integer then it is rounded up to the nearest integer. The preferred pairwise alignment algorithm is the Needleman-Wunsch global alignment algorithm [Needlman &Wunsch (1970) *J. Mol. Biol.* 48, 443-453], using default parameters (*e.g.*, with Gap opening penalty = 10.0, and with Gap extension penalty = 0.5, using the EBLOSUM62 scoring matrix). This algorithm is conveniently implemented in the *needle* tool in the EMBOSS package [Rice *et al.* (2000) *Trends Genet.* 16:276-277].

The nucleic acids and polypeptides of the inention may additionally have further sequences to the N-terminus/5′ and/or C-terminus/3′ of these sequences (a) to (d).

All of the Gram positive bacterial sequences referenced herein are publicly available through PubMed on GenBank.

Streptococcus pneumoniae Adhesin Island Sequences

As discussed above, a *S. pneumoniae* AI sequence is present in the TIGR4 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences are set forth below.

SrtD (Sp0468) is a sortase. An example of an amino acid sequence of SrtD is set forth in SEQ ID NO: 80.

SEQ ID NO: 80

MSRTKLRALLGYLLMLVACLIPIYCFGQMVLQSLGQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLASQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

SrtC (Sp0467) is a sortase. An example of an amino acid sequence of SrtC is set forth in SEQ ID NO: 81.

SEQ ID NO: 81

MSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAFNATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIG
YVEIPAIDQEIPMYVGTSEDILQKGAGLLEGASLPVGGENTHTVITAHRGLPTAELFSQLDKMKKGDIFYLHVLD
QVLAYQVDQIVTVEPNDFEPVLIQHGEDYATLLTCTPYMINSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWL
LLGAMAVILLLLYRVYRNRRIVKGLEKQLEGRHVKD

SrtB (SP0466) is a sortase. An example of an amino acid sequence of SrtB is set forth in SEQ ID NO: 82.

SEQ ID NO: 82

MAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDSLNNVVSGDPWSEEMKKKGRAEYARM
LEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTHAVITAHTGLPTAKMFTDLTKLKVGD
KFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINTHRLLVRGHRIPYVAEVEEEFIAANK
LSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVEDGQQ

Sp0465 is a hypothetical protein. An example of an amino acid sequence of Sp0465 is set forth in SEQ ID NO: 83.

PCT/US05/27239

SEQ ID NO: 83

MFLPFLSASLYLQTHHFIAFPNRQSYLLRETRKSHFFLIHHPF

RrgC (SP0464) is a cell wall surface anchor family protein. RrgC contains a sortase substrate motif VPXTG (SEQ ID NO: 137), shown in italics in SEQ ID NO: 84.

SEQ ID NO: 84

MISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRVQIVRDLHS
WDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAKKTDTMTTK
VKLIKVDQDHNRLEGVGFKLVSVARDVSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGNYRFKEVEP
LAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVLQNGKEVVV
TSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRID*VPDTG*EETLYILML
VAILLFGSGYYLTKKPNN

RrgB (Sp0463) is a cell wall surface anchor protein. RrgB contains a sortase substrate motif IPXTG (SEQ ID NO: 133), shown in italics in SEQ ID NO: 85.

SEQ ID NO: 85

MKSINKFLTMLAALLLTASSLFSAATVFAAGTTTTSVTVHKLLATDGDMDKIANELETGNYAGNKVGVLPANAKE
IAGVMFVWTNTNNEIIDENGQTLGVNIDPQTFKLSGAMPATAMKKLTEAEGAKFNTANLPAAKYKIYEIHSLSTY
VGEDGATLTGSKAVPIEIELPLNDVVDAHVYPKNTEAKPKIDKDFKGKANPDTPRVDKDTPVNHQVGDVVEYEIV
TKIPALANYATANWSDRMTEGLAFNKGTVKVTVDDVALEAGDYALTEVATGFDLKLTDAGLAKVNDQNAEKTVKI
TYSATLNDKAIVEVPESNDVTFNYGNNPDHGNTPKPNKPNENGDLTLTKTWVDATGAPIPAGAEATFDLVNAQTG
KVVQTVTLTTDKNTVTVNGLDKNTEYKFVERSIKGYSADYQEITTAGEIAVKNWKDENPKPLDPTEPKVVTYGKK
FVKVNDKDNRLAGAEFVIANADNAGQYLARKADKVSQEEKQLVVTTKDALDRAVAAYNALTAQQQTQQEKEKVDK
AQAAYNAAVIAANNAFEWVADKDNENVVKLVSDAQGRFEITGLLAGTYYLEETKQPAGYALLTSRQKFEVTATSY
SATGQGIEYTAGSGKDDATKVVNKKIT*IPQTGG*IGTIIFAVAGAAIMGIAVYAYVKNNKDEDQLA

RrgA (Sp0462) is a cell wall surface anchor protein. RrgA contains a sortase substrate motif YPXTG (SEQ ID NO: 186), indicated in italics in SEQ ID NO: 86.

SEQ ID NO: 86

MLNRETHMKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDG
TTVSQRTEAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGT
YPDVQTPYQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTVYEQKDKSVPL
DVVILLDNSNSMSNIRNKNARRAERAGEATRSLIDKITSDSENRVALVTYASTIFDGTEFTVEKGVADKNGKRLN
DSLFWNYDQTSFTTNTKDYSYLKLTNDKNDIVELKNKVPTEAEDHDGNRLMYQFGATFTQKALMKADEILTQQAR
QNSQKVIFHITDGVPTMSYPINFNHATFAPSYQNQLNAFFSKSPNKDGILLSDFITQATSGEHTIVRGDGQSYQM
FTDKTVYEKGAPAAFPVKPEKYSEMKAAGYAVIGDPINGGYIWLNWRESILAYPFNSNTAKITNHGDPTRWYYNG
NIAPDGYDVFTVGIGINGDPGTDEATATSFMQSISSKPENYTNVTDTTKILEQLNRYFHTIVTEKKSIENGTITD
PMGELIDLQLGTDGRFDPADYTLTANDGSRLENGQAVGGPQNDGGLLKNAKVLYDTTEKRIRVTGLYLGTDEKVT
LTYNVRLNDEFVSNKFYDTNGRTTLHPKEVEQNTVRDFPIPKIRDVRKYPEITISKEKKLGDIEFIKVNKNDKKP
LRGAVFSLQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVN
GEVRDVTSIVPQDIPAGYEFTNDKHYITNEPIPPKRE*YPRTG*GIGMLPFYLIGCMMMGGVLLYTRKHP

RlrA (Sp0461) is a transcriptional regulator. An example of an amino acid sequence for RlrA is set forth in SEQ ID NO: 87.

SEQ ID NO: 87

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

As discussed above, a *S. pneumoniae* AI sequence is present in the *S. pneumoniae* strain 670 genome. Examples of *S. pneumoniae* AI sequences are set forth below.

Orf1_670 is a transposase. An example of an amino acid sequence of orf1_670 is set forth in SEQ ID NO: 171.

SEQ ID NO: 171

MEHINHTTLLIGIKDKNITLNKAIQHDTHIEVFATLDYHPPKCKHCKGKQIKYDFQKPSKIPFIEIGGFPSLIHL
KKRRFQCKSCRKVTVAETTLVQKNCQISEMVRQKIAQLLLNREALTHIASKLAISTSTSTVYRKLKQFHFQEDYT
TLPEILSWDEFSYQKGKLAFIAQDFNTKKIMTILDNRRQTTIRNHFFKYSKEARKKVKVVTVDMSGSYIPLIKKL
FPNAKIVLDRFHIVQHMSRALNQTRINIMKQFDDKSLEYRALKYYWKFILKDSRKLSLKPFYARTFRETLTPREC
LKKIFTLVPELKDYYDLYQLLLFHLQEKNTDQFWGLIQDTLPHLNRTFKTTLSTFICYKNYITNAIELPYSNAKL
EATNKLIKDIKRNAFGFRNFENFKKRIFIALNIKKERTKFVLSRA

Orf2_670 is a transcriptional regulator. An example of an amino acid sequence of Orf2_670 is set forth in SEQ ID NO: 172.

SEQ ID NO: 172

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

Orf3_670 is a cell wall surface anchor family proten. An example of an amino acid sequence of Orf3_670 is set forth in SEQ ID NO: 173.

SEQ ID NO: 173

MLNRETHMKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDG
TTVSQRTEAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGT
YPDVQTPYQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPL
DVVILLDNSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILN
DSALWTFDRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQAR
PNSKKVIFHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQM
FTKKPVTDQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMA
QDGYDVFTVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMG
ELIDFQLGADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTY
NVRLNDQFVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRD
AVFSLQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEV
RDVTSIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

Orf4_670 is a cell wall surface anchor family protein. An example of an amino acid sequence of orf4_670 is set forth in SEQ ID NO: 174.

SEQ ID NO: 174

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK
DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP
NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN
ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGNNGFNLKLTEAGLAKINGKDADQKIQITYSATLN
SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE
NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE
NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY
VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV
VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDQLA

Orf5_670 is a cell wall surface anchor family protein. An example of an amino acid sequence of orf5_670 is set forth in SEQ ID NO: 175.

SEQ ID NO: 175

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK

KTDTMTTKVKETRVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN
YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL
QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKPNN

Orf6_670 is a sortase. An example of an amino acid sequence of orf6_670 is set forth in SEQ ID NO: 176.

SEQ ID NO: 176

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

Orf7_670 is a sortase. An example of an amino acid sequence of orf7_670 is set forth in SEQ ID NO: 177.

SEQ ID NO: 177

VSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAFNATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIG
YVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGENTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLD
QVLAYQVDQILTVEPNDFEPVLIQHGEDYATLLTCTPYMINSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWL
LLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

Orf8_670 is a sortase. An example of an amino acid sequence of orf8_670 is set forth in SEQ ID NO: 178.

SEQ ID NO: 178

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 19A Hungary 6 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 19A Hungary 6 are set forth below.

ORF2_19AH is a transcriptional regulator. An example of an amino acid sequence of ORF2_19AH is set forth in SEQ ID NO: 187.

SEQ ID NO: 187

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_19AH is a cell wall surface protein. An example of an amino acid sequence of ORF3_19AH is set forth in SEQ ID NO: 188.

SEQ ID NO: 188

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD
NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF
DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI
FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT

DQYGVHQILSTTSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF
TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL
GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ
FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK
QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV
PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKNP

ORF4_19AH is a cell wall surface protein. An example of an amino acid sequence of ORF4_19AH is set forth in SEQ ID NO: 189.

SEQ ID NO: 189

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK
DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP
NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN
ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGXNGFNLKLTEAGLAKINGKDADQKIQITYSATLN
SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE
NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE
NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY
VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV
VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDQLA

ORF5_19AH is a cell wall surface protein. An example of an amino acid sequence of ORF5_19AH is set forth in SEQ ID NO: 190.

SEQ ID NO: 190

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK
KTDTMTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN
YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL
QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKPNN

ORF6_19AH is a putative sortase. An example of an amino acid sequence of ORF6_19AH is set forth in SEQ ID NO: 191.

SEQ ID NO: 191

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

ORF7_19AH is a putative sortase. An example of an amino acid sequence of ORF7_19AH is set forth in SEQ ID NO: 192.

SEQ ID NO: 192

MDNSRRSRKKGTKKKKHPLILLLIFLVGFAVAIYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF
NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE
NTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLDQVLAYQVDQILTVEPNDFEPVLIQHGEDYATLLTCTPYM
INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

ORF8_19AH is a putative sortase. An example of an amino acid sequence of ORF8_19AH is set forth in SEQ ID NO: 193.

SEQ ID NO: 193

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFMGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 6B Finland 12 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 6B Finland 12 are set forth below.

ORF2_6BF is a transcriptional regulator. An example of an amino acid sequence of ORF2_6BF is set forth in SEQ ID NO: 194.

SEQ ID NO: 194

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_6BF is a cell wall surface protein. An example of an amino acid sequence of ORF3_6BF is set forth in SEQ ID NO: 195.

SEQ ID NO: 195

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD
NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF
DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI
FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT
DQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF
TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL
GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ
FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK
QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV
PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_6BF is a cell wall surface protein. An example of an amino acid sequence of ORF4_6BF is set forth in SEQ ID NO: 196.

SEQ ID NO: 196

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK
DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP
NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN
ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGNNGFNLKLTEAGLAKINGKDADQKIQITYSATLN
SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE
NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE
NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY
VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV
VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDQLA

ORF5_6BF is a cell wall surface protein. An example of an amino acid sequence of ORF5_6BF is set forth in SEQ ID NO: 197.

SEQ ID NO: 197

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK
KTDTMTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN
YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL
QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKPNN

ORF6_6BF is a putative sortase. An example of an amino acid sequence of ORF6_6BF is set forth in SEQ ID NO: 198.

SEQ ID NO: 198

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

ORF7_6BF is a putative sortase. An example of an amino acid sequence of ORF7_6BF is set forth in SEQ ID NO: 199.

SEQ ID NO: 199

MDNSRRSRKKGTKKKKHPLILLLLIFLVGFAVAIYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF
NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE
NTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLDQVLAYQVDQILTVEPNDFEPVLIQHGEDYATLLTCTPYM
INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

ORF8_6BF is a putative sortase. An example of an amino acid sequence of ORF8_6BF is set forth in SEQ ID NO: 200.

SEQ ID NO: 200

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 6B Spain 2 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 6B Spain 2 are set forth below.

ORF2_6BSP is a transcriptional regulator. An example of an amino acid sequence of ORF2_6BSP is set forth in SEQ ID NO: 201.

SEQ ID NO: 201

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_6BSP is a cell wall surface protein. An example of an amino acid sequence of ORF3_6BSP is set forth in SEQ ID NO: 202.

SEQ ID NO: 202

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD
NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF
DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI
FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT
DQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF
TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL
GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ
FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK
QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV
PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_6BSP is a cell wall surface protein. An example of an amino acid sequence of ORF4_6BSP is set forth in SEQ ID NO: 203.

SEQ ID NO: 203

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK
DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP
NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN
ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGNNGFNLKLTEAGLAKINGKDADQKIQITYSATLN
SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE
NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE
NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY
VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV
VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDQLA

ORF5_6BSP is a cell wall surface protein. An example of an amino acid sequence of ORF5_6BSP is set forth in SEQ ID NO: 204.

SEQ ID NO: 204

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK
KTDTMTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN
YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL
QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKPNN

ORF6_6BSP is a putative sortase. An example of an amino acid sequence of ORF6_6BSP is set forth in SEQ ID NO: 205.

SEQ ID NO: 205

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

ORF7_6BSP is a putative sortase. An example of an amino acid sequence of ORF7_6BSP is set forth in SEQ ID NO: 206.

SEQ ID NO: 206

MDNSRRSRKKGTKKKKHPLILLLLIFLVGFAVAIYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF
NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE
NTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLDQVLAYQVDQILTVEPNDFEPVLIQHGEDYATLLTCTPYM
INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

ORF8_6BSP is a putative sortase. An example of an amino acid sequence of ORF8_6BSP is set forth in SEQ ID NO: 207.

SEQ ID NO: 207

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 9V Spain 3 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 9V Spain 3 are set forth below.

ORF2_9VSP is a transcriptional regulator. An example of an amino acid sequence of ORF2_9VSP is set forth in SEQ ID NO: 208.

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SEQ ID NO: 208

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_9VSP is a cell wall surface protein. An example of an amino acid sequence of ORF3_9VSP is set forth in SEQ ID NO: 209.

SEQ ID NO: 209

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTNGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQRTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTVYERKDKSVPLDVVILLD
NSNSMSNIRNKNARRAERAGEATRSLIDKITSDPENRVALVTYASTIFDGTEFTVEKGVADKNGKRLNDSLFWNY
DQTSFTTNTKDYSYLKLTNDKNDIVELKNKVPTEAEDHDGNRLMYQFGATFTQKALMKADEILTQQARQNSQKVI
FHITDGVPTMSYPINFNHATFAPSYQNQLNAFFSKSPNKDGILLSDFITQATSGEHTIVRGDGQSYQMFTDKTVY
EKGAPAAFPVKPEKYSEMKAVGYAVIGDPINGGYIWLNWRESILAYPFNSNTAKITNHGDPTRWYYNGNIAPDGY
DVFTVGIGINGDPGTDEATATSFMQSISSKPENYTNVTDTTKILEQLNRYFHTIVTEKKSIENGTITDPMGELID
LQLGTDGRFDPADYTLTANDGSRLENGQAVGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRL
NDQFVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPAITIAKEKKLGEIEFIKINKNDKKPLRDAVFS
LQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVT
SIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLLFYLIGCMMMGGVLLYTRKHP

ORF4_9VSP is a cell wall surface protein. An example of an amino acid sequence of ORF4_9VSP is set forth in SEQ ID NO: 210.

SEQ ID NO: 210

MKSINKFLTMLAALLLTASSLFSAATVFAAGTTTTSVTVHKLLATDGDMDKIANELETGNYAGNKVGVLPANAKE
IAGVMFVWTNTNNEIIDENGQTLGVNIDPQTFKLSGAMPATAMKKLTEAEGAKFNTANLPAAKYKIYEIHSLSTY
VGEDGATLTGSKAVPIEIELPLNDVVDAHVYPKNTEAKPKIDKDFKGKANPDTPRVDKDTPVNHQVGDVVEYEIV
TKIPALANYATANWSDRMTEGLAFNKGTVKVTVDDVALEAGDYALTEVATGFDLKLTDAGLAKVNDQNAEKTVKI
TYSATLNDKAIVEVPESNDVTFNYGNNPDHGNTPKPNKPNENGDLTLTKTWVDATGAPIPAGAEATFDLVNAQTG
KVVQTVTLTTDKNTVTVNGLDKNTEYKFVERSIKGYSADYQEITTAGEIAVKNWKDENPKPLDPTEPKVVTYGKK
FVKVNDKDNRLAGAEFVIANADNAGQYLARKADKVSQEEKQLVVTTKDALDRAVAAYNALTAQQQTQQEKEKVDK
AQAAYNAAVIAANNAFEWVADKDNENVVKLVSDAQGRFEITGLLAGTYYLEETKQPAGYALLTSRQKFEVTATSY
SATGQGIEYTAGSGKDDATKVVNKKITIPQTGGIGTIIFAVAGAVIMGIAVYAYVKNNKDEDQLA

ORF5_9VSP is a cell wall surface protein. An example of an amino acid sequence of ORF5_9VSP is set forth in SEQ ID NO: 211.

SEQ ID NO: 211

MTMQKMQKMQKMQKMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVW
KLDDSYSYDNRVQIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMT
DQTVEPLVIVAKKADTVTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKN
GEIVVTNLPLGTYRFKEVEPLAGYTVTTMDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKV
MKEENGHYTPVLQNGKEVVVASGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNN
KRPRIDVPDTGEETLYILMLVAILLFGSGYYLTKKTNN

ORF6_9VSP is a putative sortase. An example of an amino acid sequence of ORF6_9VSP is set forth in SEQ ID NO: 212.

SEQ ID NO: 212

MLIKMAKTKKQKRNNLLLGVVFFIGIAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPAIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKRQSERALKALKEATKEVKVE
DE

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ORF7_9VSP is a putative sortase. An example of an amino acid sequence of ORF7_9VSP is set forth in SEQ ID NO: 213.

SEQ ID NO: 213

MSKSRYSRKKSVKKKKNPFILLLIFLVGLAVAMYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF
NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE
NTHTVVTAHRGLPTAELFSQLDKMKKGDIFYLHVLDQVLAYQVDQIVTVEPNDFEPVLIQHGEDYATLLTCTPYM
INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLGAMAVILLLLYRVYRNRRIVKGLEKQLEGRHVKD

ORF8_9VSP is a putative sortase. An example of an amino acid sequence of ORF8_9VSP is set forth in SEQ ID NO: 214.

SEQ ID NO: 214

MSRTKLRALLGYLLMLVACLIPIYCFGQMVLQSLGQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLASQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 14 CSR 10 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 14 CSR 10 are set forth below.

ORF2_14CSR is a transcriptional regulator. An example of an amino acid sequence of ORF2_14CSR is set forth in SEQ ID NO: 215.

SEQ ID NO: 215

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_14CSR is a cell wall surface protein. An example of an amino acid sequence of ORF3_14CSR is set forth in SEQ ID NO: 216.

SEQ ID NO: 216

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD
NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF
DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI
FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT
DQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF
TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL
GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ
FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK
QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV
PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_14CSR is a cell wall surface protein. An example of an amino acid sequence of ORF4_14CSR is set forth in SEQ ID NO: 217.

SEQ ID NO: 217

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK
DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP
NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN
ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGNNGFNLKLTEAGLAKINGKDADQKIQITYSATLN
SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE

NNWEYTWSGLDNSTEIKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE
NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY
VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV
VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDQLA

ORF5_14CSR is a cell wall surface protein. An example of an amino acid sequence of ORF5_14CSR is set forth in SEQ ID NO: 218.

SEQ ID NO: 218

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK
KTDTMTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN
YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL
QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKPNN

ORF6_14CSR is a putative sortase. An example of an amino acid sequence of ORF6_14CSR is set forth in SEQ ID NO: 219.

SEQ ID NO: 219

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

ORF7_14CSR is a putative sortase. An example of an amino acid sequence of ORF7_14CSR is set forth in SEQ ID NO: 220.

SEQ ID NO: 220

MDNSRRSRKKGTKKKKHPLILLLIFLVGFAVAIYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF
NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE
NTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLDQVLAYQVDQILTVEPNDFEPVLIQHGEDYATLLTCTPYM
INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

ORF8_14CSR is a putative sortase. An example of an amino acid sequence of ORF8_14CSR is set forth in SEQ ID NO: 221.

SEQ ID NO: 221

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 19F Taiwan 14 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 19F Taiwan 14 are set forth below.

ORF2_19FTW is a transcriptional regulator. An example of an amino acid sequence of ORF2_19FTW is set forth in SEQ ID NO: 222.

SEQ ID NO: 222

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

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ORF3_19FTW is a cell wall surface protein. An example of an amino acid sequence of ORF3_19FTW is set forth in SEQ ID NO: 223.

SEQ ID NO: 223

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTVYERKDKSVPLDVVILLD
NSNSMSNIRNKNARRAERAGEATRSLIDKITSDPENRVALVTYASTIFDGTEFTVEKGVADKNGKRLNDSLFWNY
DQTSFTTNTKDYSYLKLTNDKNDIVELKNKVPTEAEDHDGNRLMYQFGATFTQKALMKADEILTQQARQNSQKVI
FHITDGVPTMSYPINFNHATFAPSYQNQLNAFFSKSPNKDGILLSDFITQATSGEHTIVRGDGQSYQMFTDKTVY
EKGAPAAFPVKPEKYSEMKAVGYAVIGDPINGGYIWLNWRESILAYPFNSNTAKITNHGAPTRWYYNGNIAPDGY
DVFTVGIGINGDPGTDEATATSFMQSISSKPENYTNVTDTTKILEQLNRYFHTIVTEKKSIENGTITDPMGELID
LQLGTDGRFDPADYTLTANDGSRLENGQAVGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRL
NDQFVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPAITIAKEKKLGEIEFIKINKNDKKPLRDAVFS
LQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVT
SIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_19FTW is a cell wall surface protein. An example of an amino acid sequence of ORF4_19FTW is set forth in SEQ ID NO: 224.

SEQ ID NO: 224

MKSINKFLTMLAALLLTASSLFSAATVFAAGTTTTSVTVHKLLATDGDMDKIANELETGNYAGNKVGVLPANAKE
IAGVMFVWTNTNNEIIDENGQTLGVNIDPQTFKLSGAMPATAMKKLTEAEGAKFNTANLPAAKYKIYEIHSLSTY
VGEDGATLTGSKAVPIEIELPLNDVVDAHVYPKNTEAKPKIDKDFKGKANPDTPRVDKDTPVNHQVGDVVEYEIV
TKIPALANYATANWSDRMTEGLAFNKGTVKVTVDDVALEAGDYALTEVATGFDLKLTDAGLAKVNDQNAEKTVKI
TYSATLNDKAIVEVPESNDVTFNYGNNPDHGNTPKPNKPNENGDLTLTKTWVDATGAPIPAGAEATFDLVNAQTG
KVVQTVTLTTDKNTVTVNGLDKNTEYKFVERSIKGYSADYQEITTAGEIAVKNWKDENPKPLDPTEPKVVTYGKK
FVKVNDKDNRLAGAEFVIANADNAGQYLARKADKVSQEEKQLVVTTKDALDRAVAAYNALTAQQQTQQEKEKVDK
AQAAYNAAVIAANNAFEWVADKDNENVVKLVSDAQGRFEITGLLAGTYYLEETKQPAGYALLTSRQKFEVTATSY
SATGQGIEYTAGSGKDDATKVVNKKITIPQTGGIGTIIFAVAGAVIMGIAVYAYVKNNKDEDQLA

ORF5_19FTW is a cell wall surface protein. An example of an amino acid sequence of ORF5_19FTW is set forth in SEQ ID NO: 225.

SEQ ID NO: 225

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDNRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK
KADTVTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIVVTNLPLGT
YRFKEVEPLAGYTVTTMDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEENGHYTPVL
QNGKEVVVASGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKTNN

ORF6_19FTW is a putative sortase. An example of an amino acid sequence of ORF6_19FTW is set forth in SEQ ID NO: 226.

SEQ ID NO: 226

MLIKMAKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPAIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKRQSERALKALKEATKEVKVE
DE

ORF7_19FTW is a putative sortase. An example of an amino acid sequence of ORF7_19FTW is set forth in SEQ ID NO: 227.

SEQ ID NO: 227

MSKSRYSRKKSVKKKKNPFILLLIFLVGLAVAMYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF
NATLKPSEILDPFTDQEKKQGVSEYANMLKVHERIGYVEIPAIEQEIPMYVGTSEDILQKGAGLLEGASLPVGGE

NPHTVITAHRGLETAELFSQIDKMKKGDIFFLHVLDQVLAYQVDQIVTVEPNDFEPVLIQHGQDYATLLTCTPYM
INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLGAMAVILLLLYRVYRNRRIVKGLEKQLEGRHVKD

ORF8_19FTW is a putative sortase. An example of an amino acid sequence of ORF8_19FTW is set forth in SEQ ID NO: 228.

SEQ ID NO: 228

MSRTKLRALLGYLLMLVACLIPIYCFGQMVLQSLGQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLASQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 23F Taiwan 15 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 23F Taiwan 15 are set forth below.

ORF2_23FTW is a transcriptional regulator. An example of an amino acid sequence of ORF2_23FTW is set forth in SEQ ID NO: 229.

SEQ ID NO: 229

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_23FTW is a cell wall surface protein. An example of an amino acid sequence of ORF3_23FTW is set forth in SEQ ID NO: 230.

SEQ ID NO: 230

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTVYEQKDKSVPLDVVILLD
NSNSMSNIRNKNARRAERAGEATRSLIDKITSDPENRVALVTYASTIFDGTEFTVEKGVADKNGKRLNDSLFWNY
DQTSFTTNTKDYSYLKLTNDKNDIVELKNKVPTEAEDHDGNRLMYQFGATFTQKALMKADEILTQQARQNSQKVI
FHITDGVPTMSYPINFNHATFAPSYQNQLNAFFSKSPNKDGILLSDFITQATSGEHTIVRGDGQSYQMFTDKTVY
EKGAPAAFPVKPEKYSEMKAAGYAVIGDPINGGYIWLNWRESILAYPFNSNTAKITNHGDPTRWYYNGNIAPDGY
DVFTVGIGINGDPGTDEATATSFMQSISSKPENYTNVTDTTKILEQLNRYFHTIVTEKKSIENGTITDPMGELID
LQLGTDGRFDPADYTLTANDGSRLENGQAVGGPQNDGGLLKNAKVLYDTTEKRIRVTGLYLGTDEKVTLTYNVRL
NDEFVSNKFYDTNGRTTLHPKEVEQNTVRDFPIPKIRDVRKYPEITISKEKKLGDIEFIKVNKNDKKPLRDAVFS
LQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVT
SIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_23FTW is a cell wall surface protein. An example of an amino acid sequence of ORF4_23FTW is set forth in SEQ ID NO: 231.

SEQ ID NO: 231

MKSINKFLTILAALLLTVSSLFSAATVFAAEQKTKTLTVHKLLMTDQELDAWNSDAITTAGYDGSQNFEQFKQLQ
GVPQGVTEISGVAFELQSYTGPQGKEQENLTNDAVWTAVNKGVTTETGVKFDTEVLQGTYRLVEVRKESTYVGPN
GKVLTGMKAVPALITLPLVNQNGVVENAHVYPKNSEDKPTATKTFDTAAGFVDPGEKGLAIGTKVPYIVTTTIPK
NSTLATAFWSDEMTEGLDYNGDVVVNYNGQPLDNSHYTLEAGHNGFILKLNEKGLEAINGKDAEATITLKYTATL
NALAVADVPEANDVTFHYGNNPGHGNTPKPNKPKNGELTITKTWADAKDAPIAGVEVTFDLVNAQTGEVVKVPGH
ETGIVLNQTNNWTFTATGLDNNTEYKFVERTIKGYSADYQTITETGKIAVKNWKDENPEPINPEEPRVKTYGKKF
VKVDQKDERLKEAQFVVKNEQGKYLALKSAAQQAVNEKAAAEAKQALDAAIAAYTNAADKNAAQAVVDAAQKTYN
DNYRAARFGYVEVERKEDALVLTSNTDGQFQISGLAAGSYTLEETKAPEGFAKLGDVKFEVGAGSWNQGDFNYLK
DVQKNDATKVVNKKITIPQTGGIGTIIFAVAGAVIMGIAVYAYVKNNKDEDQLA

ORF5_23FTW is a cell wall surface protein. An example of an amino acid sequence of ORF5_23FTW is set forth in SEQ ID NO: 232.

SEQ ID NO: 232

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDNRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK
KADTVTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIVVTNLPLGT
YRFKEVEPLAGYTVTTMDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEENGHYTPVL
QNGKEVVVASGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKTNN

ORF6_23FTW is a putative sortase. An example of an amino acid sequence of ORF6_23FTW is set forth in SEQ ID NO: 233.

SEQ ID NO: 233

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGQLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

ORF7_23FTW is a putative sortase. An example of an amino acid sequence of ORF7_23FTW is set forth in SEQ ID NO: 234.

SEQ ID NO: 234

MDNSRRSRKKGTKKKKHPLILLLLIFLVGFAVAIYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF
NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE
NTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLDQVLAYQVDQILTVEPNDFEPVLIQHGKDYATLLTCTPYM
INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

ORF8_23FTW is a putative sortase. An example of an amino acid sequence of ORF8_23FTW is set forth in SEQ ID NO: 235.

SEQ ID NO: 235

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 23F Poland 16 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 23F Poland 16 are set forth below.

ORF2_23FP is a transcriptional regulator. An example of an amino acid sequence of ORF2_23FP is set forth in SEQ ID NO: 236.

SEQ ID NO: 236

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_23FP is a cell wall surface protein. An example of an amino acid sequence of ORF3_23FP is set forth in SEQ ID NO: 237.

SEQ ID NO: 237

MKRVRKIEQKAVAGLCCISQLIAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD
NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF
DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI
FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT
DQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF
TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL
GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ
FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK
QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV
PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKNP

ORF4_23FP is a cell wall surface protein. An example of an amino acid sequence of ORF4_23FP is set forth in SEQ ID NO: 238.

SEQ ID NO: 238

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK
DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP
NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN
ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGINGFNLKLTEAGLAKINGKDADQKIQITYSATLN
SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE
NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINLEEPRVKTYGKKFVKVDQKDTRLE
NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY
VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV
VNKKITIPQTGGIGTIIFAVAGAVIMGIAVYAYVKNNKDEDQLA

ORF5_23FP is a cell wall surface protein. An example of an amino acid sequence of ORF5_23FP is set forth in SEQ ID NO: 239.

SEQ ID NO: 239

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDNRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK
KADTVTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIVVTNLPLGT
YRFKEVEPLAGYAVTTMDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEENGHYTPVL
QNGKEVVVASGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKTNN

ORF6_23FP is a putative sortase. An example of an amino acid sequence of ORF6_23FP is set forth in SEQ ID NO: 240.

SEQ ID NO: 240

MLIKMAKTKKQKRNNLLLGVVFFIGIAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPAIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKRQSERALKALKEATKEVKVE
DE

ORF7_23FP is a putative sortase. An example of an amino acid sequence of ORF7_23FP is set forth in SEQ ID NO: 241.

SEQ ID NO: 241

MSKSRYSRKKSVKKKKNPFILLLIFLVGLAVAMYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF
NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE
NTHTVVTAHRGLPTAELFSQLDKMKKGDIFYLHVLDQVLAYQVDQIVTVEPNDFEPVLIQHGEDYATLLTCTPYM
INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLGAMAVILLLLYRVYRNRRIVKGLEKQLEGRHVKD

ORF8_23FP is a putative sortase. An example of an amino acid sequence of ORF8_23FP is set forth in SEQ ID NO: 242.

SEQ ID NO: 242 PCT/US2005/027239

MSRTKLRALLGYLLMLVACLIPIYCFGQMVLQSLGQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLASQNRIVDP
FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

Immunogenic compositions of the invention comprising AI antigens may further comprise one or more antigenic agents. Preferred antigens include those listed below. Additionally, the compositions of the present invention may be used to treat or prevent infections caused by any of the below-listed microbes. Antigens for use in the immunogenic compositions include, but are not limited to, one or more of the following set forth below, or antigens derived from one or more of the following set forth below:

Bacterial Antigens

N. meningitides: a protein antigen from *N. meningitides* serogroup A, C, W135, Y, and/or B (1-7); an outer-membrane vesicle (OMV) preparation from *N. meningitides* serogroup B. (8, 9, 10, 11); a saccharide antigen, including LPS, from *N. meningitides* serogroup A, B, C W135 and/or Y, such as the oligosaccharide from serogroup C (see PCT/US99/09346; PCT IB98/01665; and PCT IB99/00103);

Streptococcus pneumoniae: a saccharide or protein antigen, particularly a saccharide from *Streptooccus pneumoniae*;

Streptococcus agalactiae: particularly, Group B streptococcus antigens;

Streptococcus pyogenes: particularly, Group A streptococcus antigens;

Enterococcus faecalis or Enterococcus faecium: Particularly a trisaccharide repeat or other *Enterococcus* derived antigens provided in US Patent No. 6,756,361;

Helicobacter pylori: including: Cag, Vac, Nap, HopX, HopY and/or urease antigen;

Bordetella pertussis: such as petussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B. pertussis*, optionally also combination with pertactin and/or agglutinogens 2 and 3 antigen;

Staphylococcus aureus: including *S. aureus* type 5 and 8 capsular polysaccharides optionally conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A, such as StaphVAX™, or antigens derived from surface proteins, invasins (leukocidin, kinases, hyaluronidase), surface factors that inhibit phagocytic engulfment (capsule, Protein A), carotenoids, catalase production, Protein A, coagulase, clotting factor, and/or membrane-damaging toxins (optionally detoxified) that lyse eukaryotic cell membranes (hemolysins, leukotoxin, leukocidin);

Staphylococcus epidermis: particularly, *S. epidermidis* slime-associated antigen (SAA);

Staphylococcus saprophyticus: (causing urinary tract infections) particularly the 160 kDa hemagglutinin of *S. saprophyticus* antigen;

Pseudomonas aeruginosa: particularly, endotoxin A, Wzz protein, *P. aeruginosa* LPS, more particularly LPS isolated from PAO1 (O5 serotype), and/or Outer Membrane Proteins, including Outer Membrane Proteins F (OprF) *(Infect Immun.* 2001 May; 69(5): 3510-3515);

PC *Bacillus anthracis* (anthrax): such as *B. anthracis* antigens (optionally detoxified) from A-components (lethal factor (LF) and edema factor (EF)), both of which can share a common B-component known as protective antigen (PA);

Moraxella catarrhalis: (respiratory) including outer membrane protein antigens (HMW-OMP), C-antigen, and/or LPS;

Yersinia pestis (plague): such as F1 capsular antigen (*Infect Immun.* 2003 Jan; 71(1)): 374-383, LPS (*Infect Immun.* 1999 Oct; 67(10): 5395), Yersinia pestis V antigen (*Infect Immun.* 1997 Nov; 65(11): 4476-4482);

Yersinia enterocolitica (gastrointestinal pathogen): particularly LPS (*Infect Immun.* 2002 August; 70(8): 4414);

Yersinia pseudotuberculosis: gastrointestinal pathogen antigens;

Mycobacterium tuberculosis: such as lipoproteins, LPS, BCG antigens, a fusion protein of antigen 85B (Ag85B) and/or ESAT-6 optionally formulated in cationic lipid vesicles (*Infect Immun.* 2004 October; 72(10): 6148), Mycobacterium tuberculosis (Mtb) isocitrate dehydrogenase associated antigens (*Proc Natl Acad Sci U S A.* 2004 Aug 24; 101(34): **12652), and/or MPT51 antigens** (*Infect Immun.* 2004 July; 72(7): 3829);

Legionella pneumophila (Legionnairs' Disease): L. pneumophila antigens -- optionally derived from cell lines with disrupted *asd* genes (*Infect Immun.* 1998 May; 66(5): 1898);

Rickettsia: including outer membrane proteins, including the outer membrane protein A and/or B (OmpB) (*Biochim Biophys Acta.* 2004 Nov 1;1702(2):145), LPS, and surface protein antigen (SPA) (*J Autoimmun.* 1989 Jun;2 Suppl:81);

E. coli: including antigens from enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAggEC), diffusely adhering *E. coli* (DAEC), enteropathogenic *E. coli* (EPEC), and/or enterohemorrhagic *E. coli* (EHEC);

Vibrio cholerae: including proteinase antigens, LPS, particularly lipopolysaccharides of Vibrio cholerae II, O1 Inaba O-specific polysaccharides, V. cholera O139, antigens of IEM108 vaccine (*Infect Immun.* 2003 Oct;71(10):5498-504), and/or Zonula occludens toxin (Zot);

Salmonella typhi (typhoid fever): including capsular polysaccharides preferably conjugates (Vi, i.e. vax-TyVi);

Salmonella typhimurium (gastroenteritis): antigens derived therefrom are contemplated for microbial and cancer therapies, including angiogenesis inhibition and modulation of flk;

Listeria monocytogenes (sytemic infections in immunocompromised or elderly people, infections of fetus): antigens derived from L. monocytogenes are preferably used as carriers/vectors for intracytoplasmic delivery of conjugates/associated compositions of the present invention;

Porphyromonas gingivalis: particularly, *P. gingivalis* outer membrane protein (OMP);

Tetanus: such as tetanus toxoid (TT) antigens, preferably used as a carrier protein in conjunction/conjugated with the compositions of the present invention;

Diphtheria: such as a diphtheria toxoid, preferably CRM_{197}, additionally antigens capable of modulating, inhibiting or associated with ADP ribosylation are contemplated for combination/co-administration/conjugation with the compositions of the present invention, the diphtheria toxoids are preferably used as carrier proteins;

Borrelia burgdorferi (Lyme disease): such as antigens associated with P39 and P13 (an integral membrane protein, *Infect Immun.* 2001 May; 69(5): 3323-3334), VlsE Antigenic Variation Protein (*J Clin Microbiol.* 1999 Dec; 37(12): 3997);

Haemophilus influenzae B: such as a saccharide antigen therefrom;

Klebsiella: such as an OMP, including OMP A, or a polysaccharide optionally conjugated to tetanus toxoid;

Neiserria gonorrhoeae: including, a Por (or porin) protein, such as PorB (*see* Zhu *et al.*, Vaccine (2004) 22:660 – 669), a transferring binding protein, such as TbpA and TbpB (See Price *et al.*, Infection and Immunity (2004) 71(1):277 – 283), a opacity protein (such as Opa), a reduction-modifiable protein (Rmp), and outer membrane vesicle (OMV) preparations (*see* Plante *et al.*, J Infectious Disease (2000) 182:848 – 855), also see *e.g.* WO99/24578, WO99/36544, WO99/57280, WO02/079243);

Chlamydia pneumoniae: particularly *C. pneumoniae* protein antigens;

Chlamydia trachomatis: including antigens derived from serotypes A, B, Ba and C are (agents of trachoma, a cause of blindness), serotypes L_1, L_2 & L_3 (associated with Lymphogranuloma venereum), and serotypes, D-K;

Treponema pallidum (Syphilis): particularly a TmpA antigen; and

Haemophilus ducreyi (causing chancroid): including outer membrane protein (DsrA).

Where not specifically referenced, further bacterial antigens of the invention may be capsular antigens, polysaccharide antigens or protein antigens of any of the above. Further bacterial antigens may also include an outer membrane vesicle (OMV) preparation. Additionally, antigens include live, attenuated, split, and/or purified versions of any of the aforementioned bacteria. The bacterial or microbial derived antigens of the present invention may be gram-negative or gram-positive and aerobic or anaerobic.

Additionally, any of the above bacterial-derived saccharides (polysaccharides, LPS, LOS or oligosaccharides) can be conjugated to another agent or antigen, such as a carrier protein (for example CRM_{197}). Such conjugation may be direct conjugation effected by reductive amination of carbonyl moieties on the saccharide to amino groups on the protein, as provided in US Patent No. 5,360,897 and *Can J Biochem Cell Biol.* 1984 May;62(5):270-5. Alternatively, the saccharides can be conjugated through a linker, such as, with succinamide or other linkages provided in *Bioconjugate Techniques,* 1996 and *CRC, Chemistry of Protein Conjugation and Cross-Linking*, 1993.

Viral Antigens

Influenza: including whole viral particles (attenuated), split, or subunit comprising hemagglutinin (HA) and/or neuraminidase (NA) surface proteins, the influenza antigens may be derived from chicken embryos or propogated on cell culture, and/or the influenza antigens are derived from influenza type A, B, and/or C, among others;

Respiratory syncytial virus (RSV): including the F protein of the A2 strain of RSV (*J Gen Virol.* 2004 Nov; 85(Pt 11):3229) and/or G glycoprotein;

Parainfluenza virus (PIV): including PIV type 1, 2, and 3, preferably containing hemagglutinin, neuraminidase and/or fusion glycoproteins;

Poliovirus: including antigens from a family of picornaviridae, preferably poliovirus antigens such as OPV or, preferably IPV;

Measles: including split measles virus (MV) antigen optionally combined with the Protollin and or antigens present in MMR vaccine;

Mumps: including antigens present in MMR vaccine;

Rubella: including antigens present in MMR vaccine as well as other antigens from Togaviridae, including dengue virus;

Rabies: such as lyophilized inactivated virus (RabAvert™);

Flaviviridae viruses: such as (and antigens derived therefrom) yelow fever virus, Japanese encephalitis virus, dengue virus (types 1, 2, 3, or 4), tick borne encephalitis virus, and West Nile virus;

Caliciviridae; antigens therefrom;

HIV: including HIV-1 or HIV-2 strain antigens, such as gag (p24gag and p55gag), env (gp160 and gp41), pol, tat, nef, rev vpu, miniproteins, (preferably p55 gag and gp140v delete) and antigens from the isolates HIV_{IIIb}, HIV_{SF2}, HIV_{LAV}, HIV_{LAI}, HIV_{MN}, HIV-1_{CM235}, HIV-1_{US4}, HIV-2; simian immunodeficiency virus (SIV) among others;

Rotavirus: including VP4, VP5, VP6, VP7, VP8 proteins (*Protein Expr Purif.* 2004 Dec;38(2):205) and/or NSP4;

Pestivirus: such as antigens from classical porcine fever virus, bovine viral diarrhoea virus, and/or border disease virus;

Parvovirus: such as parvovirus B19;

Coronavirus: including SARS virus antigens, particularly spike protein or proteases therefrom, as well as antigens included in WO 04/92360;

Hepatitis A virus: such as inactivated virus;

Hepatitis B virus: such as the surface and/or core antigens (sAg), as well as the presurface sequences, pre-S1 and pre-S2 (formerly called pre-S), as well as combinations of the above, such as sAg/pre-S1, sAg/pre-S2, sAg/pre-S1/pre-S2, and pre-S1/pre-S2, (see, e.g., AHBV Vaccines - *Human Vaccines and Vaccination*, pp. 159-176; and U.S. Patent Nos. 4,722,840, 5,098,704, 5,324,513;

Beames et al., *J. Virol.* (1995) 69:6833-6838, Birnbaum et al., *J. Virol.* (1990) 64:3319-3330; and Zhou et al., *J. Virol.* (1991) 65:5457-5464);

Hepatitis C virus: such as E1, E2, E1/E2 (see, Houghton et al., *Hepatology* (1991) 14:381), NS345 polyprotein, NS 345-core polyprotein, core, and/or peptides from the nonstructural regions (International Publication Nos. WO 89/04669; WO 90/11089; and WO 90/14436);

Delta hepatitis virus (HDV): antigens derived therefrom, particularly δ-antigen from HDV (see, e.g., U.S. Patent No. 5,378,814);

Hepatitis E virus (HEV); antigens derived therefrom;

Hepatitis G virus (HGV); antigens derived therefrom;

Varicella zoster virus: antigens derived from varicella zoster virus (VZV) (*J. Gen. Virol.* (1986) 67:1759);

Epstein-Barr virus: antigens derived from EBV (Baer et al., *Nature* (1984) 310:207);

Cytomegalovirus: CMV antigens, including gB and gH (*Cytomegaloviruses* (J.K. McDougall, ed., Springer-Verlag 1990) pp. 125-169);

Herpes simplex virus: including antigens from HSV-1 or HSV-2 strains and glycoproteins gB, gD and gH (McGeoch et al., *J. Gen. Virol.* (1988) 69:1531 and U.S. Patent No. 5,171,568);

Human Herpes Virus: antigens derived from other human herpesviruses such as HHV6 and HHV7; and

HPV: including antigens associated with or derived from human papillomavirus (HPV), for example, one or more of E1 – E7, L1, L2, and fusions thereof, particularly the compositions of the invention may include a virus-like particle (VLP) comprising the L1 major capsid protein, more particular still, the HPV antigens are protective against one or more of HPV serotypes 6, 11, 16 and/or 18.

Further provided are antigens, compostions, methods, and microbes included in *Vaccines*, 4th Edition (Plotkin and Orenstein ed. 2004); *Medical Microbiology* 4th Edition (Murray et al. ed. 2002); *Virology*, 3rd Edition (W.K. Joklik ed. 1988); *Fundamental Virology*, 2nd Edition (B.N. Fields and D.M. Knipe, eds. 1991), which are contemplated in conjunction with the compositions of the present invention.

Additionally, antigens include live, attenuated, split, and/or purified versions of any of the aforementioned viruses.

Fungal Antigens

Fungal antigens for use herein, associated with vaccines include those described in: U.S. Pat. Nos. 4,229,434 and 4,368,191 for prophylaxis and treatment of trichopytosis caused by Trichophyton mentagrophytes; U.S. Pat. Nos. 5,277,904 and 5,284,652 for a broad spectrum dermatophyte vaccine for the prophylaxis of dermatophyte infection in animals, such as guinea pigs, cats, rabbits, horses and lambs, these antigens comprises a suspension of killed *T. equinum,* T. mentagrophytes (var. granulare), *M. canis* and/or *M. gypseum* in an effective amount optionally combined with an adjuvant;

U.S. Pat. Nos. 5,453,273 and 6,132,735 for a ringworm vaccine comprising an effective amount of a homogenized, formaldehyde-killed fungi, i.e., *Microsporum canis* culture in a carrier; U.S. Pat. No. 5,948,413 involving extracellular and intracellular proteins for pythiosis. Additional antigens identified within antifungal vaccines include Ringvac bovis LTF-130 and Bioveta.

Further, fungal antigens for use herein may be derived from Dermatophytres, including: *Epidermophyton floccusum, Microsporum audouini, Microsporum canis, Microsporum distortum, Microsporum equinum, Microsporum gypsum, Microsporum nanum, Trichophyton concentricum, Trichophyton equinum, Trichophyton gallinae, Trichophyton gypseum, Trichophyton megnini, Trichophyton mentagrophytes, Trichophyton quinckeanum, Trichophyton rubrum, Trichophyton schoenleini, Trichophyton tonsurans, Trichophyton verrucosum, T. verrucosum* var. album, var. discoides, var. ochraceum, *Trichophyton violaceum,* and/or *Trichophyton faviforme.*

Fungal pathogens for use as antigens or in derivation of antigens in conjunction with the compositions of the present invention comprise *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus, Aspergillus sydowi, Aspergillus flavatus, Aspergillus glaucus, Blastoschizomyces capitatus, Candida albicans, Candida enolase, Candida tropicalis, Candida glabrata, Candida krusei, Candida parapsilosis, Candida stellatoidea, Candida kusei, Candida parakwsei, Candida lusitaniae, Candida pseudotropicalis, Candida guilliermondi, Cladosporium carrionii, Coccidioides immitis, Blastomyces dermatidis, Cryptococcus neoformans, Geotrichum clavatum, Histoplasma capsulatum, Klebsiella pneumoniae, Paracoccidioides brasiliensis, Pneumocystis carinii, Pythiumn insidiosum, Pityrosporum ovale, Sacharomyces cerevisae, Saccharomyces boulardii, Saccharomyces pombe, Scedosporium apiosperum, Sporothrix schenckii, Trichosporon beigelii, Toxoplasma gondii, Penicillium marneffei,* Malassezia spp., Fonsecaea spp., Wangiella spp., Sporothrix spp., Basidiobolus spp., Conidiobolus spp., Rhizopus spp, Mucor spp, Absidia spp, Mortierella spp, Cunninghamella spp, and Saksenaea spp.

Other fungi from which antigens are derived include Alternaria spp, Curvularia spp, Helminthosporium spp, Fusarium spp, Aspergillus spp, Penicillium spp, Monolinia spp, Rhizoctonia spp, Paecilomyces spp, Pithomyces spp, and Cladosporium spp.

Processes for producing a fungal antigens are well known in the art (see US Patent No. 6,333,164). In a preferred method a solubilized fraction extracted and separated from an insoluble fraction obtainable from fungal cells of which cell wall has been substantially removed or at least partially removed, characterized in that the process comprises the steps of: obtaining living fungal cells; obtaining fungal cells of which cell wall has been substantially removed or at least partially removed; bursting the fungal cells of which cell wall has been substantially removed or at least partially removed; obtaining an insoluble fraction; and extracting and separating a solubilized fraction from the insoluble fraction.

In particular embodiments, microbes (bacteria, viruses and/or fungi) against which the present compositions and methods can be implement include those that cause sexually transmitted diseases (STDs) and/or those that display on their surface an antigen that can be the target or antigen composition of the invention. In a preferred embodiment of the invention, compositions are combined with antigens derived from a viral or bacterial STD. Antigens derived from bacteria or viruses can be administered in conjunction with the compositions of the present invention to provide protection against at least one of the following STDs, among others: chlamydia, genital herpes, hepatitis (particularly HCV), genital warts, gonorrhoea, syphilis and/or chancroid (See, WO00/15255).

In another embodiment the compositions of the present invention are co-administered with an antigen for the prevention or treatment of an STD.

Antigens derived from the following viruses associated with STDs, which are described in greater detail above, are preferred for co-administration with the compositions of the present invention: hepatitis (particularly HCV), HPV, HIV, or HSV.

Additionally, antigens derived from the following bacteria associated with STDs, which are described in greater detail above, are preferred for co-administration with the compositions of the present invention: *Neiserria gonorrhoeae, Chlamydia pneumoniae, Chlamydia trachomatis, Treponema pallidum*, or *Haemophilus ducreyi.*

Respiratory Antigens

The antigen may be a respiratory antigen and could further be used in an immunogenic composition for methods of preventing and/or treating infection by a respiratory pathogen, including a virus, bacteria, or fungi such as respiratory syncytial virus (RSV), PIV, SARS virus, influenza, *Bacillus anthracis,* particularly by reducing or preventing infection and/or one or more symptoms of respiratory virus infection. A composition comprising an antigen described herein, such as one derived from a respiratory virus, bacteria or fungus is administered in conjunction with the compositions of the present invention to an individual which is at risk of being exposed to that particular respiratory microbe, has been exposed to a respiratory microbe or is infected with a respiratory virus, bacteria or fungus. The composition(s) of the present invention is/are preferably co-administered at the same time or in the same formulation with an antigen of the respiratory pathogen. Administration of the composition results in reduced incidence and/or severity of one or more symptoms of respiratory infection.

Pediatric/Geriatric Antigens

In one embodiment the compositions of the present invention are used in conjunction with an antigen for treatment of a pediatric population, as in a pediatric antigen. In a more particular embodiment the pediatric population is less than about 3 years old, or less than about 2 years, or less than about 1 years old. In another embodiment the pediatric antigen (in conjunction with the composition of the present invention) is administered multiple times over at least 1, 2, or 3 years.

In another embodiment the compositions of the present invention are used in conjunction with an antigen for treatment of a geriatric population, as in a geriatric antigen.

Other Antigens

Other antigens for use in conjunction with the compositions of the present include hospital acquired (nosocomial) associated antigens.

In another embodiment, parasitic antigens are contemplated in conjunction with the compositions of the present invention. Examples of parasitic antigens include those derived from organisms causing malaria and/or Lyme disease.

In another embodiment, the antigens in conjunction with the compositions of the present invention are associated with or effective against a mosquito born illness. In another embodiment, the antigens in conjunction with the compositions of the present invention are associated with or effective against encephalitis. In another embodiment the antigens in conjunction with the compositions of the present invention are associated with or effective against an infection of the nervous system.

In another embodiment, the antigens in conjunction with the compositions of the present invention are antigens transmissible through blood or body fluids.

Antigen Formulations

In other aspects of the invention, methods of producing microparticles having adsorbed antigens are provided. The methods comprise: (a) providing an emulsion by dispersing a mixture comprising (i) water, (ii) a detergent, (iii) an organic solvent, and (iv) a biodegradable polymer selected from the group consisting of a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and a polycyanoacrylate. The polymer is typically present in the mixture at a concentration of about 1% to about 30% relative to the organic solvent, while the detergent is typically present in the mixture at a weight-to-weight detergent-to-polymer ratio of from about 0.00001:1 to about 0.1:1 (more typically about 0.0001:1 to about 0.1:1, about 0.001:1 to about 0.1:1, or about 0.005:1 to about 0.1:1); (b) removing the organic solvent from the emulsion; and (c) adsorbing an antigen on the surface of the microparticles. In certain embodiments, the biodegradable polymer is present at a concentration of about 3% to about 10% relative to the organic solvent.

Microparticles for use herein will be formed from materials that are sterilizable, non-toxic and biodegradable. Such materials include, without limitation, poly(α-hydroxy acid), polyhydroxybutyric acid, polycaprolactone, polyorthoester, polyanhydride, PACA, and polycyanoacrylate. Preferably, microparticles for use with the present invention are derived from a poly(α-hydroxy acid), in particular, from a poly(lactide) ("PLA") or a copolymer of D,L-lactide and glycolide or glycolic acid, such as a poly(D,L-lactide-co-glycolide) ("PLG" or "PLGA"), or a copolymer of D,L-lactide and caprolactone. The microparticles may be derived from any of various polymeric starting materials which have a variety of molecular weights and, in the case of the copolymers such as PLG, a variety of lactide:glycolide ratios, the selection of which will be largely a

matter of choice, depending in part on the coadministered macromolecule. These parameters are discussed more fully below.

Further antigens may also include an outer membrane vesicle (OMV) preparation.

Additional formulation methods and antigens (especially tumor antigens) are provided in U.S. Patent Serial No. 09/581,772.

Antigen References

The following references include antigens useful in conjunction with the compositions of the present invention:

1 International patent application WO99/24578
2 International patent application WO99/36544.
3 International patent application WO99/57280.
4 International patent application WO00/22430.
5 Tettelin et al. (2000) Science 287:1809-1815.
6 International patent application WO96/29412.
7 Pizza et al. (2000) Science 287:1816-1820.
8 PCT WO 01/52885.
9 Bjune et al. (1991) Lancet 338(8775).
10 Fuskasawa et al. (1999) Vaccine 17:2951-2958.
11 Rosenqist et al. (1998) Dev. Biol. Strand 92:323-333.
12 Constantino et al. (1992) Vaccine 10:691-698.
13 Constantino et al. (1999) Vaccine 17:1251-1263.
14 Watson (2000) Pediatr Infect Dis J 19:331-332.
15 Rubin (20000) Pediatr Clin North Am 47:269-285,v.
16 Jedrzejas (2001) Microbiol Mol Biol Rev 65:187-207.
17 International patent application filed on 3rd July 2001 claiming priority from GB-0016363.4;WO 02/02606; PCT IB/01/00166.
18 Kalman et al. (1999) Nature Genetics 21:385-389.
19 Read et al. (2000) Nucleic Acids Res 28:1397-406.
20 Shirai et al. (2000) J. Infect. Dis 181(Suppl 3):S524-S527.
21 International patent application WO99/27105.
22 International patent application WO00/27994.
23 International patent application WO00/37494.
24 International patent application WO99/28475.
25 Bell (2000) Pediatr Infect Dis J 19:1187-1188.
26 Iwarson (1995) APMIS 103:321-326.
27 Gerlich et al. (1990) Vaccine 8 Suppl:S63-68 & 79-80.
28 Hsu et al. (1999) Clin Liver Dis 3:901-915.
29 Gastofsson et al. (1996) N. Engl. J. Med. 334-:349-355.
30 Rappuoli et al. (1991) TIBTECH 9:232-238.
31 Vaccines (1988) eds. Plotkin & Mortimer. ISBN 0-7216-1946-0.
32 Del Guidice et al. (1998) Molecular Aspects of Medicine 19:1-70.
33 International patent application WO93/018150.
34 International patent application WO99/53310.
35 International patent application WO98/04702.
36 Ross et al. (2001) Vaccine 19:135-142.
37 Sutter et al. (2000) Pediatr Clin North Am 47:287-308.
38 Zimmerman & Spann (1999) Am Fan Physician 59:113-118, 125-126.
39 Dreensen (1997) Vaccine 15 Suppl"S2-6.
40 MMWR Morb Mortal Wkly rep 1998 Jan 16:47(1):12, 9.
41 McMichael (2000) Vaccine19 Suppl 1:S101-107.

42 Schuchat (1999) Lancet 353(9146):51-6.
43 GB patent applications 0026333.5, 0028727.6 & 0105640.7.
44 Dale (1999) Infect Disclin North Am 13:227-43, viii.
45 Ferretti et al. (2001) PNAS USA 98: 4658-4663.
46 Kuroda et al. (2001) Lancet 357(9264):1225-1240; see also pages 1218-1219.
47 Ramsay et al. (2001) Lancet 357(9251):195-196.
48 Lindberg (1999) Vaccine 17 Suppl.2:S28-36.
49 Buttery & Moxon (2000) J R Coil Physicians Long 34:163-168.
50 Ahmad & Chapnick (1999) Infect Dis Clin North Am 13:113-133, vii.
51 Goldblatt (1998) J. Med. Microbiol. 47:663-567.
52 European patent 0 477 508.
53 U.S. Patent No. 5,306,492.
54 International patent application WO98/42721.
55 Conjugate Vaccines (eds. Cruse et al.) ISBN 3805549326, particularly vol. 10:48-114.
56 Hermanson (1996) Bioconjugate Techniques ISBN: 012323368 & 012342335X.
57 European patent application 0372501.
58 European patent application 0378881.
59 European patent application 0427347.
60 International patent application WO93/17712.
61 International patent application WO98/58668.
62 European patent application 0471177.
63 International patent application WO00/56360.
64 International patent application WO00/67161.

The contents of all of the above cited patents, patent applications and journal articles are incorporated by reference as if set forth fully herein.

There may be an upper limit to the number of Gram positive bacterial proteins which will be in the compositions of the invention. Preferably, the number of Gram positive bacterial proteins in a composition of the invention is less than 20, less than 19, less than 18, less than 17, less than 16, less than 15, less than 14, less than 13, less than 12, less than 11, less than 10, less than 9, less than 8, less than 7, less than 6, less than 5, less than 4, or less than 3. Still more preferably, the number of Gram positive bacterial proteins in a composition of the invention is less than 6, less than 5, or less than 4. Still more preferably, the number of Gram positive bacterial proteins in a composition of the invention is 3.

The Gram positive bacterial proteins and polynucleotides used in the invention are preferably isolated, *i.e.*, separate and discrete, from the whole organism with which the molecule is found in nature or, when the polynucleotide or polypeptide is not found in nature, is sufficiently free of other biological macromolecules so that the polynucleotide or polypeptide can be used for its intended purpose.

Fusion Proteins: GBS AI sequences

The GBS AI proteins used in the invention may be present in the composition as individual separate polypeptides, but it is preferred that at least two (*i.e.* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) of the antigens are expressed as a single polypeptide chain (a "hybrid" or "fusion" polypeptide). Such fusion polypeptides offer two principal advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable fusion partner that

overcomes the problem: second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically useful.

The fusion polypeptide may comprise one or more AI polypeptide sequences. Preferably, the fusion comprises an AI surface protein sequence. Preferably, the fusion polypeptide includes one or more of GBS 80, GBS 104, and GBS 67. Most preferably, the fusion peptide includes a polypeptide sequence from GBS 80. Accordingly, the invention includes a fusion peptide comprising a first amino acid sequence and a second amino acid sequence, wherein said first and second amino acid sequences are selected from a GBS AI surface protein or a fragment thereof. Preferably, the first and second amino acid sequences in the fusion polypeptide comprise different epitopes.

Hybrids (or fusions) consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten GBS antigens are preferred. In particular, hybrids consisting of amino acid sequences from two, three, four, or five GBS antigens are preferred.

Different hybrid polypeptides may be mixed together in a single formulation. Within such combinations, a GBS antigen may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

Hybrid polypeptides can be represented by the formula **NH_2-A-{-X-L-}$_n$-B-COOH**, wherein: X is an amino acid sequence of a GBS AI protein or a fragment thereof; L is an optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and *n* is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of X_1 will be retained, but the leader peptides of X_2 ... X_n will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X_1 as moiety -A-.

For each *n* instances of {-X-L-}, linker amino acid sequence -L- may be present or absent. For instance, when *n*=2 the hybrid may be NH_2-X_1-L_1-X_2-L_2-COOH, NH_2-X_1-X_2-COOH, NH_2-X_1-L_1-X_2-COOH, NH_2-X_1-X_2-L_2-COOH, *etc.* Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* comprising Gly_n where $n = 2, 3, 4, 5, 6, 7, 8, 9, 10$ or more), and histidine tags (*i.e.* His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG, with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site, thus aiding cloning and manipulation, and the $(Gly)_4$ tetrapeptide being a typical poly-glycine linker.

-A- is an optional N-terminal amino acid sequence. This will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19,

18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (*e.g.* histidine tags *i.e.* His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X_1 lacks its own N-terminus methionine, -A- is preferably an oligopeptide (*e.g.* with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine.

-B- is an optional C-terminal amino acid sequence. This will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (*e.g.* comprising histidine tags *i.e.* His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

Most preferably, n is 2 or 3.

Fusion Proteins: Gram positive bacteria AI sequences

The Gram positive bacteria AI proteins used in the invention may be present in the composition as individual separate polypeptides, but it is preferred that at least two (*i.e.* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) of the antigens are expressed as a single polypeptide chain (a "hybrid" or "fusion" polypeptide). Such fusion polypeptides offer two principal advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable fusion partner that overcomes the problem; second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically useful.

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Hybrids (or fusions) consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten Gram positive bacteria antigens are preferred. In particular, hybrids consisting of amino acid sequences from two, three, four, or five Gram positive bacteria antigens are preferred.

Different hybrid polypeptides may be mixed together in a single formulation. Within such combinations, a Gram positive bacteria AI sequence may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

Hybrid polypeptides can be represented by the formula $\mathbf{NH_2\text{-}A\text{-}\{\text{-}X\text{-}L\text{-}\}_n\text{-}B\text{-}COOH}$, wherein: X is an amino acid sequence of a Gram positive bacteria AI sequence or a fragment thereof; L is an

optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and *n* is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of X_1 will be retained, but the leader peptides of X_2 ... X_n will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X_1 as moiety -A-.

For each *n* instances of {-X-L-}, linker amino acid sequence -L- may be present or absent. For instance, when *n*=2 the hybrid may be NH_2-X_1-L_1-X_2-L_2-COOH, NH_2-X_1-X_2-COOH, NH_2-X_1-L_1-X_2-COOH, NH_2-X_1-X_2-L_2-COOH, *etc.* Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* comprising Gly_n where $n = 2, 3, 4, 5, 6, 7, 8, 9, 10$ or more), and histidine tags (*i.e.* His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG, with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site, thus aiding cloning and manipulation, and the $(Gly)_4$ tetrapeptide being a typical poly-glycine linker.

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-B- is an optional C-terminal amino acid sequence. This will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (*e.g.* comprising histidine tags *i.e.* His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

Most preferably, *n* is 2 or 3.

Antibodies: GBS AI sequences

The GBS AI proteins of the invention may also be used to prepare antibodies specific to the GBS AI proteins. The antibodies are preferably specific to the an oligomeric or hyper-oligomeric form of an AI protein. The invention also includes combinations of antibodies specific to GBS AI proteins selected to provide protection against an increased range of GBS serotypes and strain isolates. For example, a combination may comprise a first and second antibody, wherein said first

antibody is specific to a first GBS AI protein and said second antibody is specific to a second GBS AI protein. Preferably, the nucleic acid sequence encoding said first GBS AI protein is not present in a GBS genome comprising a polynucleotide sequence encoding for said second GBS AI protein. Preferably, the nucleic acid sequence encoding said first and second GBS AI proteins are present in the genomes of multiple GBS serotypes and strain isolates.

The GBS specific antibodies of the invention include one or more biological moieties that, through chemical or physical means, can bind to or associate with an epitope of a GBS polypeptide. The antibodies of the invention include antibodies which specifically bind to a GBS AI protein. The invention includes antibodies obtained from both polyclonal and monoclonal preparations, as well as the following: hybrid (chimeric) antibody molecules (see, for example, Winter *et al.* (1991) *Nature* 349: 293-299; and US Patent No. 4,816,567; $F(ab')_2$ and F(ab) fragments; F_v molecules (non-covalent heterodimers, see, for example, Inbar *et al.* (1972) *Proc Natl Acad Sci USA* 69:2659-2662; and Ehrlich *et al.* (1980) *Biochem* 19:4091-4096); single-chain Fv molecules (sFv) (see, for example, Huston *et al.* (1988) *Proc Natl Acad Sci USA* 85:5897-5883); dimeric and trimeric antibody fragment constructs; minibodies (see, *e.g.*, Pack *et al.* (1992) *Biochem* 31:1579-1584; Cumber *et al.* (1992) *J Immunology* 149B: 120-126); humanized antibody molecules (see, for example, Riechmann *et al.* (1988) *Nature* 332:323-327; Verhoeyan *et al.* (1988) *Science* 239:1534-1536; and U.K. Patent Publication No. GB 2,276,169, published 21 September 1994); and, any functional fragments obtained from such molecules, wherein such fragments retain immunological binding properties of the parent antibody molecule. The invention further includes antibodies obtained through non-conventional processes, such as phage display.

Preferably, the GBS specific antibodies of the invention are monoclonal antibodies. Monoclonal antibodies of the invention include an antibody composition having a homogeneous antibody population. Monoclonal antibodies of the invention may be obtained from murine hybridomas, as well as human monoclonal antibodies obtained using human rather than murine hybridomas. See, *e.g.*, Cote, *et al. Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, 1985, p 77.

The antibodies of the invention may be used in diagnostic applications, for example, to detect the presence or absence of GBS in a biological sample. The antibodies of the invention may also be used in the prophylactic or therapeutic treatment of GBS infection.

Antibodies: Gram positive bacteria AI sequences

The Gram positive bacteria AI proteins of the invention may also be used to prepare antibodies specific to the Gram positive bacteria AI proteins. The antibodies are preferably specific to the an oligomeric or hyper-oligomeric form of an AI protein. The invention also includes combinations of antibodies specific to Gram positive bacteria AI proteins selected to provide protection against an increased range of Gram positive bacteria genus, species, serotypes and strain isolates.

For example, a combination may comprise a first and second antibody, wherein said first antibody is specific to a first Gram positive bacteria AI protein and said second antibody is specific to a second Gram positive bacteria AI protein. Preferably, the nucleic acid sequence encoding said first Gram positive bacteria AI protein is not present in a Gram positive bacterial genome comprising a polynucleotide sequence encoding for said second Gram positive bacteria AI protein. Preferably, the nucleic acid sequence encoding said first and second Gram positive bacteria AI proteins are present in the genomes of multiple Gram positive bacteria genus, species, serotypes or strain isolates.

As an example of an instance where the combination of antibodies provides protection against an increased range of bacteria serotypes, the first antibody may be specific to a first GAS AI protein and the second antibody may be specific to a second GAS AI protein. The first GAS AI protein may comprise a GAS AI-1 surface protein, while the second GAS AI protein may comprise a GAS AI-2 or AI-3 surface protein.

As an example of an instance where the combination of antibodies provides protection against an increased range of bacterial species, the first antibody may be specific to a GBS AI protein and the second antibody may be specific to a GAS AI protein. Alternatively, the first antibody may be specific to a GAS AI protein and the second antibody may be specific to a *S. pneumoniae* AI protein.

The Gram positive specific antibodies of the invention include one or more biological moieties that, through chemical or physical means, can bind to or associate with an epitope of a Gram positive bacteria AI polypeptide. The antibodies of the invention include antibodies which specifically bind to a Gram positive bacteria AI protein. The invention includes antibodies obtained from both polyclonal and monoclonal preparations, as well as the following: hybrid (chimeric) antibody molecules (see, for example, Winter *et al.* (1991) *Nature* 349: 293-299; and US Patent No. 4,816,567; $F(ab')_2$ and F(ab) fragments; F_v molecules (non-covalent heterodimers, see, for example, Inbar *et al.* (1972) *Proc Natl Acad Sci USA* 69:2659-2662; and Ehrlich *et al.* (1980) *Biochem* 19:4091-4096); single-chain Fv molecules (sFv) (see, for example, Huston *et al.* (1988) *Proc Natl Acad Sci USA* 85:5897-5883); dimeric and trimeric antibody fragment constructs; minibodies (see, *e.g.*, Pack *et al.* (1992) *Biochem* 31:1579-1584; Cumber *et al.* (1992) *J Immunology* 149B: 120-126); humanized antibody molecules (see, for example, Riechmann *et al.* (1988) *Nature* 332:323-327; Verhoeyan *et al.* (1988) *Science* 239:1534-1536; and U.K. Patent Publication No. GB 2,276,169, published 21 September 1994); and, any functional fragments obtained from such molecules, wherein such fragments retain immunological binding properties of the parent antibody molecule. The invention further includes antibodies obtained through non-conventional processes, such as phage display.

Preferably, the Gram positive specific antibodies of the invention are monoclonal antibodies. Monoclonal antibodies of the invention include an antibody composition having a homogeneous antibody population. Monoclonal antibodies of the invention may be obtained from murine hybridomas, as well as human monoclonal antibodies obtained using human rather than murine

hybridomas. See *e.g.* Cote, *et al. Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, 1985, p 77.

The antibodies of the invention may be used in diagnostic applications, for example, to detect the presence or absence of Gram positive bacteria in a biological sample. The antibodies of the invention may also be used in the prophylactic or therapeutic treatment of Gram positive bacteria infection.

Nucleic Acids

The invention provides nucleic acids encoding the Gram positive bacteria sequences and/or the hybrid fusion polypeptides of the invention. The invention also provides nucleic acid encoding the GBS antigens and/or the hybrid fusion polypeptides of the invention. Furthermore, the invention provides nucleic acid which can hybridise to these nucleic acids, preferably under "high stringency" conditions (*e.g.* 65°C in a 0.1xSSC, 0.5% SDS solution).

Polypeptides of the invention can be prepared by various means (*e.g.* recombinant expression, purification from cell culture, chemical synthesis, *etc.*) and in various forms (*e.g.* native, fusions, non-glycosylated, lipidated, *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other GAS or host cell proteins).

Nucleic acid according to the invention can be prepared in many ways (*e.g.* by chemical synthesis, from genomic or cDNA libraries, from the organism itself, *etc.*) and can take various forms (*e.g.* single stranded, double stranded, vectors, probes, *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other GBS or host cell nucleic acids).

The term "nucleic acid" includes DNA and RNA, and also their analogues, such as those containing modified backbones (*e.g.* phosphorothioates, *etc.*), and also peptide nucleic acids (PNA), *etc.* The invention includes nucleic acid comprising sequences complementary to those described above (*e.g.* for antisense or probing purposes).

The invention also provides a process for producing a polypeptide of the invention, comprising the step of culturing a host cell transformed with nucleic acid of the invention under conditions which induce polypeptide expression.

The invention provides a process for producing a polypeptide of the invention, comprising the step of synthesising at least part of the polypeptide by chemical means.

The invention provides a process for producing nucleic acid of the invention, comprising the step of amplifying nucleic acid using a primer-based amplification method (*e.g.* PCR).

The invention provides a process for producing nucleic acid of the invention, comprising the step of synthesising at least part of the nucleic acid by chemical means.

Purification and Recombinant Expression

The Gram positive bacteria AI proteins of the invention may be isolated from the native Gram positive bacteria, or they may be recombinantly produced, for instance in a heterologous host. For example, the GAS, GBS, and *S. pneumoniae* antigens of the invention may be isolated from

Streptococcus agalactiae, S. pyogenes, S. pneumoniae, or they may be recombinantly produced, for instance, in a heterologous host. Preferably, the GBS antigens are prepared using a heterologous host.

The heterologous host may be prokaryotic (*e.g.* a bacterium) or eukaryotic. It is preferably *E.coli*, but other suitable hosts include *Bacillus subtilis, Vibrio cholerae, Salmonella typhi, Salmonella typhimurium, Neisseria lactamica, Neisseria cinerea, Mycobacteria* (*e.g. M.tuberculosis*), *S. gordonii*, *L. lactis*, yeasts, *etc.*

Recombinant production of polypeptides is facilitated by adding a tag protein to the Gram positive bacteria AI sequence to be expressed as a fusion protein comprising the tag protein and the Gram positive bacteria antigen. For example, recombinant production of polypeptides is facilitated by adding a tag protein to the GBS antigen to be expressed as a fusion protein comprising the tag protein and the GBS antigen. Such tag proteins can facilitate purification, detection and stability of the expressed protein. Tag proteins suitable for use in the invention include a polyarginine tag (Arg-tag), polyhistidine tag (His-tag), FLAG-tag, Strep-tag, c-myc-tag, S-tag, calmodulin-binding peptide, cellulose-binding domain, SBP-tag,, chitin-binding domain, glutathione S-transferase-tag (GST), maltose-binding protein, transcription termination anti-terminiantion factor (NusA), *E. coli* thioredoxin (TrxA) and protein disulfide isomerase I (DsbA). Preferred tag proteins include His-tag and GST. A full discussion on the use of tag proteins can be found at Terpe et al., "Overview of tag protein fusions: from molecular and biochemical fundamentals to commercial systems", Appl Microbiol Biotechnol (2003) 60:523 – 533.

After purification, the tag proteins may optionally be removed from the expressed fusion protein, *i.e.*, by specifically tailored enzymatic treatments known in the art. Commonly used proteases include enterokinase, tobacco etch virus (TEV), thrombin, and factor X_a.

GBS polysaccharides

The compositions of the invention may be further improved by including GBS polysaccharides. Preferably, the GBS antigen and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide provide protection from different GBS serotypes.

The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other.

Thus the invention provides an immunogenic composition comprising (i) one or more GBS AI proteins and (ii) one or more GBS saccharide antigens. The polypeptide and the polysaccharide may advantageously be covalently linked to each other to form a conjugate.

Between them, the combined polypeptide and saccharide antigens preferably cover (or provide protection from) two or more GBS serotypes (*e.g.* 2, 3, 4, 5, 6, 7, 8 or more serotypes). The serotypes of the polypeptide and saccharide antigens may or may not overlap. For example, the polypeptide might protect against serogroup II or V, while the saccharide protects against either serogroups Ia, Ib, or III. Preferred combinations protect against the following groups of serotypes:

(1) serotypes Ia and Ib, (2) serotypes Ia and II, (3) serotypes Ia and III, (4) serotypes Ia and IV, (5) serotypes Ia and V, (6) serotypes Ia and VI, (7) serotypes Ia and VII, (8) serotypes Ia and VIII, (9) serotypes Ib and II, (10) serotypes Ib and III, (11) serotypes Ib and IV, (12) serotypes Ib and V, (13) serotypes Ib and VI, (14) serotypes Ib and VII, (15) serotypes Ib and VIII, 16) serotypes II and III, (17) serotypes II and IV, (18) serotypes II and V, (19) serotypes II and VI, (20) serotypes II and VII, (21) serotypes II and VII, (22) serotypes III and IV, (23) serotypes III and V, (24) serotypes III and VI, (25) serotypes III and VII, (26) serotypes III and VIII, (27) serotypes IV and V, (28) serotypes IV and VI, (29) serotypes IV and VII, (30) serotypes IV and VIII, (31) serotypes V and VI, (32) serotypes V and VII, (33) serotypes V and VIII, (34) serotypes VI and VII, (35) serotypes VI and VIII, and (36) serotypes VII and VIII.

Still more preferably, the combinations protect against the following groups of serotypes: (1) serotypes Ia and II, (2) serotypes Ia and V, (3) serotypes Ib and II, (4) serotypes Ib and V, (5) serotypes III and II, and (6) serotypes III and V. Most preferably, the combinations protect against serotypes III and V.

Protection against serotypes II and V is preferably provided by polypeptide antigens. Protection against serotypes Ia, Ib and/or III may be polypeptide or saccharide antigens.

Immunogenic compositions and medicaments

Compositions of the invention are preferably immunogenic compositions, and are more preferably vaccine compositions. The pH of the composition is preferably between 6 and 8, preferably about 7. The pH may be maintained by the use of a buffer. The composition may be sterile and/or pyrogen-free. The composition may be isotonic with respect to humans.

Vaccines according to the invention may either be prophylactic (*i.e.* to prevent infection) or therapeutic (*i.e.* to treat infection), but will typically be prophylactic. Accordingly, the invention includes a method for the therapeutic or prophylactic treatment of a Gram positive bacteria infection in an animal susceptible to such gram positive bacterial infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic composition of the invention. For example, the invention includes a method for the therapeutic or prophylactic treatment of a *Streptococcus agalactiae*, *S. pyogenes*, or *S. pneumoniae* infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic compositions of the invention.

The invention also provides a composition of the invention for use of the compositions described herein as a medicament. The medicament is preferably able to raise an immune response in a mammal (*i.e.* it is an immunogenic composition) and is more preferably a vaccine.

The invention also provides the use of the compositions of the invention in the manufacture of a medicament for raising an immune response in a mammal. The medicament is preferably a vaccine.

The invention also provides kits comprising one or more containers of compositions of the invention. Compositions can be in liquid form or can be lyophilized, as can individual antigens. Suitable containers for the compositions include, for example, bottles, vials, syringes, and test tubes.

Containers can be formed from a variety of materials, including glass or plastic. A container may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The composition may comprise a first component comprising one or more Gram positive bacteria AI proteins. Preferably, the AI proteins are surface AI proteins. Preferably, the AI surface proteins are in an oligomeric or hyperoligomeric form. For example, the first component comprises a combination of GBS antigens or GAS antigens, or *S. pneumoniae* antigens. Preferably said combination includes GBS 80. Preferably GBS 80 is present in an oligomeric or hyperoligomeric form.

The kit can further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution, or dextrose solution. It can also contain other materials useful to the end-user, including other buffers, diluents, filters, needles, and syringes. The kit can also comprise a second or third container with another active agent, for example an antibiotic.

The kit can also comprise a package insert containing written instructions for methods of inducing immunity against S agalactiae andor *S. pyogenes* and/or *S pneumoniae* or for treating S agalactiae andor *S. pyogenes* and/or S pneumoniae infections. The package insert can be an unapproved draft package insert or can be a package insert approved by the Food and Drug Administration (FDA) or other regulatory body.

The invention also provides a delivery device pre-filled with the immunogenic compositions of the invention.

The invention also provides a method for raising an immune response in a mammal comprising the step of administering an effective amount of a composition of the invention. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. This immune response will preferably induce long lasting (*e.g.*, neutralising) antibodies and a cell mediated immunity that can quickly respond upon exposure to one or more GBS and/or GAS and/or *S. pneumoniae* antigens. The method may raise a booster response.

The invention provides a method of neutralizing GBS, GAS, or *S. pneumoniae* infection in a mammal comprising the step of administering to the mammal an effective amount of the immunogenic compositions of the invention, a vaccine of the invention, or antibodies which recognize an immunogenic composition of the invention.

The mammal is preferably a human. Where the vaccine is for prophylactic use, the human is preferably a female (either of child bearing age or a teenager). Alternatively, the human may be elderly (e.g., over the age of 50, 55, 60, 65, 70 or 75) and may have an underlying disease such as diabetes or cancer. Where the vaccine is for therapeutic use, the human is preferably a pregnant female or an elderly adult.

These uses and methods are preferably for the prevention and/or treatment of a disease caused by *Streptococcus agalactiae*, or *S. pyogenes*, or *S. pneumoniae*. The compositions may also be

effective against other streptococcal bacteria. The compositions may also be effective against other Gram positive bacteria.

One way of checking efficacy of therapeutic treatment involves monitoring Gram positive bacterial infection after administration of the composition of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses against the Gram positive bacterial antigens in the compositions of the invention after administration of the composition.

One way of checking efficacy of therapeutic treatment involves monitoring GBS infection after administration of the composition of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses against the GBS antigens in the compositions of the invention after administration of the composition.

A way of assessing the immunogenicity of the component proteins of the immunogenic compositions of the present invention is to express the proteins recombinantly and to screen patient sera or mucosal secretions by immunoblot. A positive reaction between the protein and the patient serum indicates that the patient has previously mounted an immune response to the protein in question- that is, the protein is an immunogen. This method may also be used to identify immunodominant proteins and/or epitopes.

Another way of checking efficacy of therapeutic treatment involves monitoring GBS or GAS or *S pneumoniae* infection after administration of the compositions of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses both systemically (such as monitoring the level of IgG1 and IgG2a production) and mucosally (such as monitoring the level of IgA production) against the GBS and/or GAS and/or *S pneumoniae* antigens in the compositions of the invention after administration of the composition. Typically, GBS and/or GAS and/or S pneumoniae serum specific antibody responses are determined post-immunization but pre-challenge whereas mucosal GBS and/or GAS and/or *S pneumoniae* specific antibody body responses are determined post-immunization and post-challenge.

The vaccine compositions of the present invention can be evaluated in *in vitro* and *in vivo* animal models prior to host, *e.g.*, human, administration.

The efficacy of immunogenic compositions of the invention can also be determined *in vivo* by challenging animal models of GBS and/or GAS and/or S pneumoniae infection, *e.g.*, guinea pigs or mice, with the immunogenic compositions. The immunogenic compositions may or may not be derived from the same serotypes as the challenge serotypes. Preferably the immunnogenic compositions are derivable from the same serotypes as the challenge serotypes. More preferably, the immunogenic composition and/or the challenge serotypes are derivable from the group of GBS and/or GAS and/or *S pneumoniae* serotypes.

In vivo efficacy models include but are not limited to: (i) A murine infection model using human GBS and/or GAS and/or S pneumoniae serotypes; (ii) a murine disease model which is a murine model using a mouse-adapted GBS and/or GAS and/or S pneumoniae strain, such as those

strains outlined above which is particularly virulent in mice and (iii) a primate model using human GBS or GAS or S pneumoniae isolates.

The immune response may be one or both of a TH1 immune response and a TH2 response.

The immune response may be an improved or an enhanced or an altered immune response.

The immune response may be one or both of a systemic and a mucosal immune response.

Preferably the immune response is an enhanced system and/or mucosal response.

An enhanced systemic and/or mucosal immunity is reflected in an enhanced TH1 and/or TH2 immune response. Preferably, the enhanced immune response includes an increase in the production of IgG1 and/or IgG2a and/or IgA

Preferably the mucosal immune response is a TH2 immune response. Preferably, the mucosal immune response includes an increase in the production of IgA.

Activated TH2 cells enhance antibody production and are therefore of value in responding to extracellular infections. Activated TH2 cells may secrete one or more of IL-4, IL-5, IL-6, and IL-10. A TH2 immune response may result in the production of IgG1, IgE, IgA and memory B cells for future protection.

A TH2 immune response may include one or more of an increase in one or more of the cytokines associated with a TH2 immune response (such as IL-4, IL-5, IL-6 and IL-10), or an increase in the production of IgG1, IgE, IgA and memory B cells. Preferably, the enhanced TH2 immune resonse will include an increase in IgG1 production.

A TH1 immune response may include one or more of an increase in CTLs, an increase in one or more of the cytokines associated with a TH1 immune response (such as IL-2, IFNγ, and TNFβ), an increase in activated macrophages, an increase in NK activity, or an increase in the production of IgG2a. Preferably, the enhanced TH1 immune response will include an increase in IgG2a production.

Immunogenic compositions of the invention, in particular, immunogenic composition comprising one or more GAS antigens of the present invention may be used either alone or in combination with other GAS antigens optionally with an immunoregulatory agent capable of eliciting a Th1 and/or Th2 response.

Compositions of the invention will generally be administered directly to a patient. Certain routes may be favored for certain compositons, as resulting in the generation of a more effective immune response, preferably a CMI response, or as being less likely to induce side effects, or as being easier for administration. Direct delivery may be accomplished by parenteral injection (*e.g.* subcutaneously, intraperitoneally, intradermally, intravenously, intramuscularly, or to the interstitial space of a tissue), or by rectal, oral (*e.g.* tablet, spray), vaginal, topical, transdermal (*e.g.* see WO 99/27961) or transcutaneous (*e.g.* see WO 02/074244 and WO 02/064162), intranasal (*e.g.* see WO03/028760), ocular, aural, pulmonary or other mucosal administration.

The invention may be used to elicit systemic and/or mucosal immunity.

In one particularly preferred embodiment, the immunogenic composition comprises one or more GBS or GAS or S pneumoniae antigen(s) which elicits a neutralising antibody response and one or more GBS or GAS or S pneumoniae antigen(s) which elicit a cell mediated immune response. In this way, the neutralising antibody response prevents or inhibits an initial GBS or GAS or S pneumoniae infection while the cell-mediated immune response capable of eliciting an enhanced Th1 cellular response prevents further spreading of the GBS or GAS or S pneumoniae infection. Preferably, the immunogenic composition comprises one or more GBS or GAS or S pneumoniae surface antigens and one or more GBS or GAS or S pneumoniae cytoplasmic antigens. Preferably the immunogenic composition comprises one or more GBS or GAS or S pneumoniae surface antigens or the like and one or other antigens, such as a cytoplasmic antigen capable of eliciting a Th1 cellular response.

Dosage treatment can be a single dose schedule or a multiple dose schedule. Multiple doses may be used in a primary immunisation schedule and/or in a booster immunisation schedule. In a multiple dose schedule the various doses may be given by the same or different routes *e.g.* a parenteral prime and mucosal boost, a mucosal prime and parenteral boost, *etc.*

The compositions of the invention may be prepared in various forms. For example, the compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared (*e.g.* a lyophilised composition). The composition may be prepared for topical administration *e.g.* as an ointment, cream or powder. The composition may be prepared for oral administration *e.g.* as a tablet or capsule, as a spray, or as a syrup (optionally flavoured). The composition may be prepared for pulmonary administration *e.g.* as an inhaler, using a fine powder or a spray. The composition may be prepared as a suppository or pessary. The composition may be prepared for nasal, aural or ocular administration *e.g.* as drops. The composition may be in kit form, designed such that a combined composition is reconstituted just prior to administration to a patient. Such kits may comprise one or more antigens in liquid form and one or more lyophilised antigens.

Immunogenic compositions used as vaccines comprise an immunologically effective amount of antigen(s), as well as any other components, such as antibiotics, as needed. By 'immunologically effective amount', it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention, or increases a measurable immune response or prevents or reduces a clinical symptom. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (*e.g.* non-human primate, primate, *etc.*), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

Further Components of the Composition

The composition of the invention will typically, in addition to the components mentioned above, comprise one or more 'pharmaceutically acceptable carriers', which include any carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition. Suitable carriers are typically large, slowly metabolised macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes). Such carriers are well known to those of ordinary skill in the art. The vaccines may also contain diluents, such as water, saline, glycerol, *etc.* Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present. A thorough discussion of pharmaceutically acceptable excipients is available in Gennaro (2000) *Remington: The Science and Practice of Pharmacy.* 20th ed., ISBN: 0683306472.

Adjuvants

Vaccines of the invention may be administered in conjunction with other immunoregulatory agents. In particular, compositions will usually include an adjuvant. Adjuvants for use with the invention include, but are not limited to, one or more of the following set forth below:

A. Mineral Containing Compositions

Mineral containing compositions suitable for use as adjuvants in the invention include mineral salts, such as aluminum salts and calcium salts. The invention includes mineral salts such as hydroxides (*e.g.* oxyhydroxides), phosphates (*e.g.* hydroxyphosphates, orthophosphates), sulfates, *etc.* (*e.g.* see chapters 8 & 9 of *Vaccine Design...* (1995) eds. Powell & Newman. ISBN: 030644867X. Plenum.), or mixtures of different mineral compounds (*e.g.* a mixture of a phosphate and a hydroxide adjuvant, optionally with an excess of the phosphate), with the compounds taking any suitable form (*e.g.* gel, crystalline, amorphous, *etc.*), and with adsorption to the salt(s) being preferred. The mineral containing compositions may also be formulated as a particle of metal salt (WO 00/23105).

Aluminum salts may be included in vaccines of the invention such that the dose of Al^{3+} is between 0.2 and 1.0 mg per dose.

B. Oil-Emulsions

Oil-emulsion compositions suitable for use as adjuvants in the invention include squalene-water emulsions, such as MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer). See WO90/14837. See also, Podda, "The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine", Vaccine (2001) 19: 2673-2680; Frey et al., "Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults", Vaccine (2003) 21:4234-4237. MF59 is used as the adjuvant in the FLUAD™ influenza virus trivalent subunit vaccine.

Particularly preferred adjuvants for use in the compositions are submicron oil-in-water emulsions. Preferred submicron oil-in-water emulsions for use herein are squalene/water emulsions optionally containing varying amounts of MTP-PE, such as a submicron oil-in-water emulsion containing 4-5% w/v squalene, 0.25-1.0% w/v Tween 80 ™ (polyoxyelthylenesorbitan monooleate), and/or 0.25-1.0% Span 85™ (sorbitan trioleate), and, optionally, N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-huydroxyphosphophoryloxy)-ethylamine (MTP-PE), for example, the submicron oil-in-water emulsion known as "MF59" (International Publication No. WO 90/14837; US Patent Nos. 6,299,884 and 6,451,325, incorporated herein by reference in their entireties; and Ott et al., "MF59 -- Design and Evaluation of a Safe and Potent Adjuvant for Human Vaccines" in *Vaccine Design: The Subunit and Adjuvant Approach* (Powell, M.F. and Newman, M.J. eds.) Plenum Press, New York, 1995, pp. 277-296). MF59 contains 4-5% w/v Squalene (e.g. 4.3%), 0.25-0.5% w/v Tween 80™, and 0.5% w/v Span 85™ and optionally contains various amounts of MTP-PE, formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA). For example, MTP-PE may be present in an amount of about 0-500 μg/dose, more preferably 0-250 μg/dose and most preferably, 0-100 μg/dose. As used herein, the term "MF59-0" refers to the above submicron oil-in-water emulsion lacking MTP-PE, while the term MF59-MTP denotes a formulation that contains MTP-PE. For instance, "MF59-100" contains 100 μg MTP-PE per dose, and so on. MF69, another submicron oil-in-water emulsion for use herein, contains 4.3% w/v squalene, 0.25% w/v Tween 80™, and 0.75% w/v Span 85™ and optionally MTP-PE. Yet another submicron oil-in-water emulsion is MF75, also known as SAF, containing 10% squalene, 0.4% Tween 80™, 5% pluronic-blocked polymer L121, and thr-MDP, also microfluidized into a submicron emulsion. MF75-MTP denotes an MF75 formulation that includes MTP, such as from 100-400 μg MTP-PE per dose.

Submicron oil-in-water emulsions, methods of making the same and immunostimulating agents, such as muramyl peptides, for use in the compositions, are described in detail in International Publication No. WO 90/14837 and US Patent Nos. 6,299,884 and 6,45 1,325, incorporated herein by reference in their entireties.

Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) may also be used as adjuvants in the invention.

C. Saponin Formulations

Saponin formulations, may also be used as adjuvants in the invention. Saponins are a heterologous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponin from the bark of the *Quillaia saponaria* Molina tree have been widely studied as adjuvants. Saponin can also be commercially obtained from *Smilax ornata* (sarsaprilla), *Gypsophilla paniculata* (brides veil), and *Saponaria officianalis* (soap root). Saponin adjuvant formulations include purified formulations, such as QS21, as well as lipid formulations, such as ISCOMs.

Saponin compositions have been purified using High Performance Thin Layer Chromatography (HP-LC) and Reversed Phase High Performance Liquid Chromatography (RP-HPLC). Specific purified fractions using these techniques have been identified, including QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. Preferably, the saponin is QS21. A method of production of QS21 is disclosed in US Patent No. 5,057,540. Saponin formulations may also comprise a sterol, such as cholesterol (see WO96/33739).

Combinations of saponins and cholesterols can be used to form unique particles called Immunostimulating Complexs (ISCOMs). ISCOMs typically also include a phospholipid such as phosphatidylethanolamine or phosphatidylcholine. Any known saponin can be used in ISCOMs. Preferably, the ISCOM includes one or more of Quil A, QHA and QHC. ISCOMs are further described in EP0109942, WO 96/11711 and WO 96/33739. Optionally, the ISCOMS may be devoid of additional detergent. See WO 00/07621.

A review of the development of saponin based adjuvants can be found at Barr, et al., "ISCOMs and other saponin based adjuvants", Advanced Drug Delivery Reviews (1998) 32:247-271. See also Sjolander, et al., "Uptake and adjuvant activity of orally delivered saponin and ISCOM vaccines", Advanced Drug Delivery Reviews (1998) 32:321-338.

D. Virosomes and Virus Like Particles (VLPs)

Virosomes and Virus Like Particles (VLPs) can also be used as adjuvants in the invention. These structures generally contain one or more proteins from a virus optionally combined or formulated with a phospholipid. They are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. The viral proteins may be recombinantly produced or isolated from whole viruses. These viral proteins suitable for use in virosomes or VLPs include proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus, Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Qß-phage (such as coat proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty protein p1). VLPs are discussed further in WO 03/024480, WO 03/024481, and Niikura et al., "Chimeric Recombinant Hepatitis E Virus-Like Particles as an Oral Vaccine Vehicle Presenting Foreign Epitopes", Virology (2002) 293:273-280; Lenz et al., "Papillomarivurs-Like Particles Induce Acute Activation of Dendritic Cells", Journal of Immunology (2001) 5246-5355; Pinto, et al., "Cellular Immune Responses to Human Papillomavirus (HPV)-16 L1 Healthy Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles", Journal of Infectious Diseases (2003) 188:327-338; and Gerber et al., "Human Papillomavrisu Virus-Like Particles Are Efficient Oral Immunogens when Coadministered with Escherichia coli Heat-Labile Entertoxin Mutant R192G or CpG", Journal of Virology (2001) 75(10):4752-4760. Virosomes are discussed further in, for example, Gluck et al., "New Technology Platforms in the Development of Vaccines for the Future", Vaccine (2002) 20:B10 –B16. Immunopotentiating reconstituted influenza virosomes (IRIV) are used as the subunit antigen

delivery system in the intranasal trivalent INFLEXAL™ product {Mischler & Metcalfe (2002) *Vaccine* 20 Suppl 5:B17-23} and the INFLUVAC PLUS™ product.

E. Bacterial or Microbial Derivatives

Adjuvants suitable for use in the invention include bacterial or microbial derivatives such as:

(1) *Non-toxic derivatives of enterobacterial lipopolysaccharide (LPS)*

Such derivatives include Monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. A preferred "small particle" form of 3 De-O-acylated monophosphoryl lipid A is disclosed in EP 0 689 454. Such "small particles" of 3dMPL are small enough to be sterile filtered through a 0.22 micron membrane (see EP 0 689 454). Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives *e.g.* RC-529. See Johnson *et al.* (1999) *Bioorg Med Chem Lett* 9:2273-2278.

(2) *Lipid A Derivatives*

Lipid A derivatives include derivatives of lipid A from *Escherichia coli* such as OM-174. OM-174 is described for example in Meraldi et al., "OM-174, a New Adjuvant with a Potential for Human Use, Induces a Protective Response with Administered with the Synthetic C-Terminal Fragment 242-310 from the circumsporozoite protein of Plasmodium berghei", Vaccine (2003) 21:2485-2491; and Pajak, et al., "The Adjuvant OM-174 induces both the migration and maturation of murine dendritic cells in vivo", Vaccine (2003) 21:836-842.

(3) *Immunostimulatory oligonucleotides*

Immunostimulatory oligonucleotides suitable for use as adjuvants in the invention include nucleotide sequences containing a CpG motif (a sequence containing an unmethylated cytosine followed by guanosine and linked by a phosphate bond). Bacterial double stranded RNA or oligonucleotides containing palindromic or poly(dG) sequences have also been shown to be immunostimulatory.

The CpG's can include nucleotide modifications/analogs such as phosphorothioate modifications and can be double-stranded or single-stranded. Optionally, the guanosine may be replaced with an analog such as 2'-deoxy-7-deazaguanosine. See Kandimalla, et al., "Divergent synthetic nucleotide motif recognition pattern: design and development of potent immunomodulatory oligodeoxyribonucleotide agents with distinct cytokine induction profiles", Nucleic Acids Research (2003) 31(9): 2393-2400; WO02/26757 and WO99/62923 for examples of possible analog substitutions. The adjuvant effect of CpG oligonucleotides is further discussed in Krieg, "CpG motifs: the active ingredient in bacterial extracts?", Nature Medicine (2003) 9(7): 831-835; McCluskie, et al., "Parenteral and mucosal prime-boost immunization strategies in mice with hepatitis B surface antigen and CpG DNA", FEMS Immunology and Medical Microbiology (2002) 32:179-185; WO98/40100; US Patent No. 6,207,646; US Patent No. 6,239,116 and US Patent No. 6,429,199.

The CpG sequence may be directed to TLR9, such as the motif GTCGTT or TTCGTT. See Kandimalla, et al., "Toll-like receptor 9: modulation of recognition and cytokine induction by novel

synthetic CpG DNAs", Biochemical Society Transactions (2003) 31 (part 3): 654-658. The CpG sequence may be specific for inducing a Th1 immune response, such as a CpG-A ODN, or it may be more specific for inducing a B cell response, such a CpG-B ODN. CpG-A and CpG-B ODNs are discussed in Blackwell, et al., "CpG-A-Induced Monocyte IFN-gamma-Inducible Protein-10 Production is Regulated by Plasmacytoid Dendritic Cell Derived IFN-alpha", J. Immunol. (2003) 170(8):4061-4068; Krieg, "From A to Z on CpG", TRENDS in Immunology (2002) 23(2): 64-65 and WO01/95935. Preferably, the CpG is a CpG-A ODN.

Preferably, the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. Optionally, two CpG oligonucleotide sequences may be attached at their 3' ends to form "immunomers". See, for example, Kandimalla, et al., "Secondary structures in CpG oligonucleotides affect immunostimulatory activity", BBRC (2003) 306:948-953; Kandimalla, et al., "Toll-like receptor 9: modulation of recognition and cytokine induction by novel synthetic GpG DNAs", Biochemical Society Transactions (2003) 31(part 3):664-658; Bhagat et al., "CpG penta- and hexadeoxyribonucleotides as potent immunomodulatory agents" BBRC (2003) 300:853-861 and WO 03/035836.

(4) *ADP-ribosylating toxins and detoxified derivatives thereof.*

Bacterial ADP-ribosylating toxins and detoxified derivatives thereof may be used as adjuvants in the invention. Preferably, the protein is derived from *E. coli* (i.e., E. coli heat labile enterotoxin "LT), cholera ("CT"), or pertussis ("PT"). The use of detoxified ADP-ribosylating toxins as mucosal adjuvants is described in WO95/17211 and as parenteral adjuvants in WO98/42375. Preferably, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LTR192G. The use of ADP-ribosylating toxins and detoxified derivaties thereof, particularly LT-K63 and LT-R72, as adjuvants can be found in the following references, each of which is specifically incorporated by reference herein in their entirety: Beignon, et al., "The LTR72 Mutant of Heat-Labile Enterotoxin of Escherichia coli Enahnces the Ability of Peptide Antigens to Elicit CD4+ T Cells and Secrete Gamma Interferon after Coapplication onto Bare Skin", Infection and Immunity (2002) 70(6):3012-3019; Pizza, et al., "Mucosal vaccines: non toxic derivatives of LT and CT as mucosal adjuvants", Vaccine (2001) 19:2534-2541; Pizza, et al., "LTK63 and LTR72, two mucosal adjuvants ready for clinical trials" Int. J. Med. Microbiol (2000) 290(4-5):455-461; Scharton-Kersten et al., "Transcutaneous Immunization with Bacterial ADP-Ribosylating Exotoxins, Subunits and Unrelated Adjuvants", Infection and Immunity (2000) 68(9):5306-5313; Ryan et al., "Mutants of Escherichia coli Heat-Labile Toxin Act as Effective Mucosal Adjuvants for Nasal Delivery of an Acellular Pertussis Vaccine: Differential Effects of the Nontoxic AB Complex and Enzyme Activity on Th1 and Th2 Cells" Infection and Immunity (1999) 67(12):6270-6280; Partidos et al., "Heat-labile enterotoxin of Escherichia coli and its site-directed mutant LTK63 enhance the proliferative and cytotoxic T-cell responses to intranasally co-immunized synthetic peptides", Immunol. Lett. (1999) 67(3):209-216; Peppoloni et al., "Mutants of the Escherichia coli heat-labile enterotoxin as safe and strong adjuvants for intranasal delivery of vaccines", Vaccines (2003) 2(2):285-293; and Pine et al., (2002) "Intranasal

immunization with influenza vaccine and a detoxified mutant of heat labile enterotoxin from Escherichia coli (LTK63)" J. Control Release (2002) 85(1-3):263-270. Numerical reference for amino acid substitutions is preferably based on the alignments of the A and B subunits of ADP-ribosylating toxins set forth in Domenighini et al., Mol. Microbiol (1995) 15(6):1165-1167, specifically incorporated herein by reference in its entirety.

F. Bioadhesives and Mucoadhesives

Bioadhesives and mucoadhesives may also be used as adjuvants in the invention. Suitable bioadhesives include esterified hyaluronic acid microspheres (Singh *et al.* (2001) *J. Cont. Rele.* 70:267-276) or mucoadhesives such as cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrollidone, polysaccharides and carboxymethylcellulose. Chitosan and derivatives thereof may also be used as adjuvants in the invention. E.g. WO99/27960.

G. Microparticles

Microparticles may also be used as adjuvants in the invention. Microparticles (*i.e.* a particle of ~100nm to ~150μm in diameter, more preferably ~200nm to ~30μm in diameter, and most preferably ~500nm to ~10μm in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly(α-hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) are preferred, optionally treated to have a negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB).

H. Liposomes

Examples of liposome formulations suitable for use as adjuvants are described in US Patent No. 6,090,406, US Patent No. 5,916,588, and EP 0 626 169.

I. Polyoxyethylene ether and Polyoxyethylene Ester Formulations

Adjuvants suitable for use in the invention include polyoxyethylene ethers and polyoxyethylene esters. WO99/52549. Such formulations further include polyoxyethylene sorbitan ester surfactants in combination with an octoxynol (WO01/21207) as well as polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol (WO 01/21152).

Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether (laureth 9), polyoxyethylene-9-steoryl ether, polyoxytheylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

J. Polyphosphazene (PCPP)

PCPP formulations are described, for example, in Andrianov et al., "Preparation of hydrogel microspheres by coacervation of aqueous polyphophazene solutions", Biomaterials (1998) 19(1-3):109-115 and Payne et al., "Protein Release from Polyphosphazene Matrices", Adv. Drug. Delivery Review (1998) 31(3):185-196.

K. Muramyl peptides

Examples of muramyl peptides suitable for use as adjuvants in the invention include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-l-alanyl-d-isoglutamine (nor-MDP), and N-acetylmuramyl-l-alanyl-d-isoglutaminyl-l-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE).

L. Imidazoquinolone Compounds.

Examples of imidazoquinolone compounds suitable for use adjuvants in the invention include Imiquamod and its homologues, described further in Stanley, "Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential" Clin Exp Dermatol (2002) 27(7):571-577 and Jones, "Resiquimod 3M", Curr Opin Investig Drugs (2003) 4(2):214-218.

The invention may also comprise combinations of aspects of one or more of the adjuvants identified above. For example, the following adjuvant compositions may be used in the invention:

(1) a saponin and an oil-in-water emulsion (WO 99/11241);

(2) a saponin (e.g.., QS21) + a non-toxic LPS derivative (e.g. 3dMPL) (see WO 94/00153);

(3) a saponin (e.g.., QS21) + a non-toxic LPS derivative (e.g. 3dMPL) + a cholesterol;

(4) a saponin (*e.g.* QS21) + 3dMPL + IL-12 (optionally + a sterol) (WO 98/57659);

(5) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions (See European patent applications 0835318, 0735898 and 0761231);

(6) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion.

(7) Ribi™ adjuvant system (RAS), (Ribi Immunochem) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™);

(8) one or more mineral salts (such as an aluminum salt) + a non-toxic derivative of LPS (such as 3dPML).

(9) one or more mineral salts (such as an aluminum salt) + an immunostimulatory oligonucleotide (such as a nucleotide sequence including a CpG motif). Combination No. (9) is a preferred adjuvant combination.

M. Human Immunomodulators

Human immunomodulators suitable for use as adjuvants in the invention include cytokines, such as interleukins (*e.g.* IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, *etc.*), interferons (*e.g.* interferon-γ), macrophage colony stimulating factor, and tumor necrosis factor.

Aluminum salts and MF59 are preferred adjuvants for use with injectable influenza vaccines. Bacterial toxins and bioadhesives are preferred adjuvants for use with mucosally-delivered vaccines, such as nasal vaccines.

The immunogenic compositions of the present invention may be administed in combination with an antibiotic treatment regime. In one embodiment, the antibiotic is administered prior to administration of the antigen of the invention or the composition comprising the one or more of the antigens of the invention.

In another embodiment, the antibiotic is administered subsequent to the adminstration of the one or more antigens of the invention or the composition comprising the one or more antigens of the invention. Examples of antibiotics suitable for use in the treatment of the Steptococcal infections of the invention include but are not limited to penicillin or a derivative thereof or clindamycin or the like.

Further antigens

The compositions of the invention may further comprise one or more additional Gram positive bacterial antigens which are not associated with an AI. Preferably, the Gram positive bacterial antigens that are not associated with an AI can provide protection across more than one serotype or strain isolate. For example, a first non-AI antigen, in which the first non-AI antigen is at least 90% (*i.e.*, at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%) homologous to the amino acid sequence of a second non-AI antigen, wherein the first and the second non-AI antigen are derived from the genomes of different serotypes of a Gram positive bacteria, may be further included in the compositions. The first non-AI antigen may also be homologous to the amino acid sequence of a third non-AI antigen, such that the first non-AI antigen, the second non-AI antigen, and the third non-AI antigen are derived from the genomes of different serotypes of a Gram positive bacteria. The first non-AI antigen may also be homologous to the amino acid sequence of a fourth non-AI antigen, such that the first non-AI antigen, the second non-AI antigen, the third non-AI antigen, and the fourth non-AI antigen are derived from the genomes of different serotypes of a Gram positive bacteria.

The first non-AI antigen may be GBS 322. The amino acid sequence of GBS 322 across GBS strains from serotypes Ia, Ib, II, III, V, and VIII is greater than 90%. Alternatively, the first non-AI antigen may be GBS 276. The amino acid sequence of GBS 276 across GBS strain from serotypes Ia, Ib, II, III, V, and VIII is greater than 90%. Table 13 provides the percent amino acid sequence identity of GBS 322 and GBS 276 across different GBS strains and serotypes.

Table 13: Conservation of GBS 322 and GBS 276 amino acid sequences

Serotype	Strains	GBS 322		GBS 276	
		cGH	%AA identity	cGH	%AA identity
Ia	**090**	+	98.60	+	97.90
	A909	+	98.30	+	97.90
	515	+	98.80	+	97.50
	DK1	+		+	
	DK8	+		+	
	Davis	+		+	
Ib	**7357b**	+		+	
	H36B	+	98.30	+	97.80
II	**18RS21**	+	100.00	+	99.90
	DK21	+		+	

Serotype	Strains	GBS 322		GBS 276	
		cGH	%AA identity	cGH	%AA identity
III	NEM316	+	100.00	+	97.00
	COH31	+		+	
	D136	+		+	
	M732	+	98.00	+	100.00
	COH1	+	98.30	+	100.00
	M781	+	98.30	+	99.60
No type	CJB110	+	98.60	+	97.90
	1169NT	+	97.40	+	97.90
V	CJB111	+	100.00	+	
	2603	+	100.00	+	100.00
VIII	JM130013	+	100.00	+	97.90
	SMU014	+		+	
total		22/22	98.28+/-0.4	22/22	98.44 +/-1.094

As an example, inclusion of a non-AI protein, GBS 322, in combination with AI antigens GBS 67, GBS 80, and GBS 104 provided protection to newborn mice in an active maternal immunization assay.

Table 14: Active maternal immunization assay for a combination of fragments from GBS 322, GBS 80, GBS 104, and GBS 67

		FACS (Δ Mean)			MIX=322+80+104+67		PBS	
GBS strains	Type	GBS 80	GBS 67	GBS 322	alive/treated	% protection	alive/treated	% protection
515	Ia	0	409	227	39/40	97	6/40	15
7357b-	Ib	91	316	102	19/30	63	1/30	3
DK21	II	0	331	416	25/34	73	17/48	35
5401	II	170	618	135	35/40	87	3/37	8
3050	II	43	460	188	48/48	100	1/30	3
COH1	III	305	0	130	36/36	100	7/40	17
M781	III	65	0	224	30/40	75	4/39	10
2603	V	125	105	313	27/33	82	10/35	28
CJB111	V	370	481	63	25/28	89	4/46	9
JM9130013	VIII	597	83	143	37/39	95	5/40	12
JMU071	VIII	556	79	170	44/50	88	18/50	36
NT1169	NT	0	443	213	12/32	37	11/35	31

In fact, the non-AI GBS 322 antigen may itself provide protection to newborn mice in an active maternal immunization assay.

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Table 16: Active maternal immunization assay for each of GBS 80 and GBS 322 antigens

		GBS 80			GBS 322		
		FACS	Protection (% survival)		FACS	Protection (% survival)	
GBS strains	Type	Δ Mean	antigen	ctrl-	Δ Mean	antigen	ctrl-
CJB111	V	370	72 %	40%	63	57%	40%
COH1	III	305	76 %	10%	130	3%	10%
2603	V	82	22 %	34%	313	83 %	34%
7357b-	Ib	91	36%	34%	102	43%	34%
18RS21	II	0	15%	24%	268	84 %	24%
DK21	II	0	10%	21%	416	67 %	25%
A909	Ia	0	0%	14%			
090	Ia	0	0%	0%			
H36B	Ib				105	34%	32%

Thus, inclusion of a non-AI protein in an immunogenic composition of the invention may provide increased protection a mammal.

The immunogenic compositions comprising *S. pneumonaie* AI polypeptides may further secondary SP protein antigens which include (a) any of the SP protein antigens disclosed in WO 02/077021 or U.S. provisional application _____, filed April 20, 2005 (Attorney Docket Number 002441.00154), (2) immunogenic portions of the antigens comprising at least 7 contiguous amino acids, (3) proteins comprising amino acid sequences which retain immunogenicity and which are at least 95% identical to these SP protein antigens (*e.g.*, 95%, 96%, 97%, 98%, 99%, or 99.5% identical), and (4) fusion proteins, including hybrid SP protein antigens, comprising (1)-(3).

Alternatively, the invention may include an immunogenic composition comprising a first and a second Gram positive bacteria non-AI protein, wherein the polynucleotide sequence encoding the sequence of the first non-AI protein is less than 90% (i.e., less than 90, 88, 86, 84, 82, 81, 78, 76, 74, 72, 70, 65, 60, 55, 50, 45, 40, 35, or 30 percent) homologous than the corresponding sequence in the genome of the second non-AI protein.

The compositions of the invention may further comprise one or more additional non-Gram positive bacterial antigens, including additional bacterial, viral or parasitic antigens. The compositions of the invention may further comprise one or more additional non-GBS antigens, including additional bacterial, viral or parasitic antigens.

In another embodiment, the GBS antigen combinations of the invention are combined with one or more additional, non-GBS antigens suitable for use in a vaccine designed to protect elderly or immunocomprised individuals. For example, the GBS antigen combinations may be combined with an antigen derived from the group consisting of *Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermis, Pseudomonas aeruginosa, Legionella pneumophila, Listeria monocytogenes, Neisseria meningitides,* influenza, and Parainfluenza virus ('PIV').

Where a saccharide or carbohydrate antigen is used, it is preferably conjugated to a carrier protein in order to enhance immunogenicity {*e.g.* Ramsay *et al.* (2001) *Lancet* 357(9251):195-196; Lindberg (1999) *Vaccine* 17 Suppl 2:S28-36; Buttery & Moxon (2000) *J R Coll Physicians Lond* 34:163-168; Ahmad & Chapnick (1999) *Infect Dis Clin North Am* 13:113-133, vii.; Goldblatt (1998) *J. Med. Microbiol.* 47:563-567; European patent 0 477 508; US Patent No. 5,306,492; International patent application WO98/42721; *Conjugate Vaccines* (eds. Cruse *et al.*) ISBN 3805549326, particularly vol. 10:48-114; and Hermanson (1996) *Bioconjugate Techniques* ISBN: 0123423368 or 012342335X}. Preferred carrier proteins are bacterial toxins or toxoids, such as diphtheria or tetanus toxoids. The CRM_{197} diphtheria toxoid is particularly preferred {*Research Disclosure*, 453077 (Jan 2002)}. Other carrier polypeptides include the *N.meningitidis* outer membrane protein (EP-A-0372501), synthetic peptides (EP-A-0378881; EP-A-0427347), heat shock proteins (WO 93/17712; WO 94/03208), pertussis proteins (WO 98/58668; EP A 0471177), protein D from *H.influenzae* (WO 00/56360), cytokines (WO 91/01146), lymphokines, hormones, growth factors, toxin A or B from *C.difficile* (WO00/61761), iron-uptake proteins (WO01/72337), *etc.* Where a mixture comprises capsular saccharides from both serogroups A and C, it may be preferred that the ratio (w/w) of MenA saccharide:MenC saccharide is greater than 1 (*e.g.* 2:1, 3:1, 4:1, 5:1, 10:1 or higher). Different saccharides can be conjugated to the same or different type of carrier protein. Any suitable conjugation reaction can be used, with any suitable linker where necessary.

Toxic protein antigens may be detoxified where necessary *e.g.* detoxification of pertussis toxin by chemical and/or genetic means.

Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens.

Antigens in the composition will typically be present at a concentration of at least 1μg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

As an alternative to using protein antigens in the composition of the invention, nucleic acid encoding the antigen may be used {*e.g.* refs. Robinson & Torres (1997) *Seminars in Immunology* 9:271-283; Donnelly *et al.* (1997) *Annu Rev Immunol* 15:617-648; Scott-Taylor & Dalgleish (2000) *Expert Opin Investig Drugs* 9:471-480; Apostolopoulos & Plebanski (2000) *Curr Opin Mol Ther* 2:441-447; Ilan (1999) *Curr Opin Mol Ther* 1:116-120; Dubensky *et al.* (2000) *Mol Med* 6:723-732; Robinson & Pertmer (2000) *Adv Virus Res* 55:1-74; Donnelly *et al.* (2000) *Am J Respir Crit Care Med* 162(4 Pt 2):S190-193; and Davis (1999) *Mt. Sinai J. Med.* 66:84-90}. Protein components of the compositions of the invention may thus be replaced by nucleic acid (preferably DNA *e.g.* in the form of a plasmid) that encodes the protein.

Definitions PCT/US05/27239

The term "comprising" means "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term "about" in relation to a numerical value *x* means, for example, $x \pm 10\%$.

References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of *Current Protocols in Molecular Biology* (F.M. Ausubel *et al.*, eds., 1987) Supplement 30. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is disclosed in Smith & Waterman (1981) *Adv. Appl. Math.* 2: 482-489.

The invention is further illustrated, without limitation, by the following examples.

EXAMPLE 1: Binding of an Adhesin Island surface protein, GBS 80, to Fibrinogen and Fibronectin.

This example demonstrates that an Adhesin Island surface protein, GBS 80 can bind to fibrinogen and fibronectin.

An enzyme-linked immunosorbent assay (ELISA) was used to analyse the *in vitro* binding ability of recombinant GBS 80 to immobilized extra-cellular matrix (ECM) proteins but not to bovine serum albumin (BSA). Microtiter plates were coated with ECM proteins (fibrinogen, fibronectin, laminin, collagen type IV) and binding assessed by adding varying concentrations of a recombinant form of GBS 80, over-expressed and purified from *E. coli* (FIGURE 5A). Plates were then incubated sequentially with a) mouse anti-GBS 80 primary antibody; b) rabbit anti-mouse AP-conjugated secondary antibody; c) pNPP colorimetric substrate. Relative binding was measured by monitoring absorbance at 405 nm, using 595 nm as a reference wavelength. Figure 5b shows binding of recombinant GBS 80 to immobilized ECM proteins (1 μg) as a function of concentration of GBS 80. BSA was used as a negative control. Data points represent the means of OD_{405} values ± standard deviation for 3 wells.

Binding of GBS 80 to the tested ECM proteins was found to be concentration dependent and exhibited saturation kinetics. As is also evident from FIGURE 5, binding of GBS 80 to fibronectin and fibrinogen was greater than binding to laminin and collagen type IV at all the concentrations tested.

EXAMPLE 2: GBS 80 is required for surface localization of GBS 104.

This example demonstrates that co-expression of GBS 80 is required for surface localization of GBS 104.

The polycistronic nature of the Adhesin Island I mRNA was investigated through reverse transcriptase-PCR (RT-PCR) analysis employing primers designed to detect transcripts arising from contiguous genes. Total RNA was isolated from GBS cultures grown to an optical density at 600 nm

(OD_{600}) of 0.3 in THB (Todd-Hewitt broth) by the RNeasy Total RNA isolation method (Qiagen) according to the manufacturer's instructions. The absence of contaminating chromosomal DNA was confirmed by failure of the gene amplification reactions to generate a product detectable by agarose gel electrophoresis, in the absence of reverse transcriptase. RT-PCR analysis was performed with the Access RT-PCR system (Promega) according to the manufacturer's instructions, employing PCR cycling temperatures of 60°C for annealing and 70°C for extension. Amplification products were visualized alongside 100-bp DNA markers in 2% agarose gels after ethidium bromide staining.

FIGURE 5 shows that all the genes are co-transcribed as an operon. A schematic of the AI-1 operon is shown above the agarose gel analysis of the RT-PCR products. Large rectangular arrows indicate the predicted transcript direction. Primer pairs were selected such as "1-4" cross the 3'finish-5'start of successive genes and overlap each gene by at least 200 bp. Additionally, "1" crosses a putative rho-independent transcriptional terminator. "5" is an internal GBS 80 control and "6" is an unrelated control from a highly expressed gene. Lanes: "a": RNA plus RTase enzyme; "b" RNA without RTase; "c": genomic DNA control.

In the effort to elucidate the functions of the AI-1 proteins, in frame deletions of all of the genes within the operon have been constructed and the resulting mutants characterized with respect to surface exposure of the encoded antigens (see FIGURE 8).

Each in-frame deletion mutation was constructed by splice overlap extension PCR (SOE-PCR) essentially as decribed by Horton et al. [Horton R. M., Z. L. Cai, S. N. Ho, L. R. Pease (1990) Biotechniques 8:528-35] using suitable primers and cloned into the temperature sensitive shuttle vector pJRS233 to replace the wild type copy by allelic exchange [Perez-Casal, J., J. A. Price, et al. (1993) Mol Microbiol 8(5): 809-19.]. All plasmid constructions utilized standard molecular biology techniques, and the identities of DNA fragments generated by PCR were verified by sequencing. Following SOE-PCR, the resulting mutant DNA fragments were digested with XhoI and EcoRI, and ligated into a similarly digested pJRS233. The resuting vectors were introduced by electroporation into the chromosome of 2603 and COH1 GBS strains in a three-step process, essentially as described in Framson et al. [Framson, P. E., A. Nittayajarn, J. Merry, P. Youngman, and C. E. Rubens. (1997) Appl. Environ. Microbiol. 63(9):3539-47]. Briefly, the vector pJRS233 contains an *erm* gene encoding erythromycin resistance and a temperature-sensitive gram-positive replicon that is active at 30°C but not at 37°C. Initially, the constructs are electroporated into GBS electro-competent cells prepared as described by Frameson et al., and transformants containing free plasmid are selected by their ability to grow at 30°C on Todd-Hewitt Broth (THB) agar plates containing 1 μg/ml erythromycin. The second step includes a selection step for strains in which the plasmid has integrated into the chromosome via a single recombination event over the homologous plasmid insert and chromosome sequence by their ability to grow at 37°C on THB agar medium containing 1 mg/ml erythromycin. In the third step, GBS cells containing the plasmid integrated within the chromosome (integrants) are serially passed in broth culture in the absence of antibiotics at 30°C. Plasmid excision

from the chromosome via a second recombination event over the duplicated target gene sequence either completed the allelic exchange or reconstituted the wild-type genotype. Subsequent loss of the plasmid in the absence of antibiotic selection pressure resulted in an erythromycin-sensitive phenotype. In order to assess gene replacement a screening of erythromycin-sensitive colonies was performed by analysis of the target gene PCR amplicons.

FIGURE 7 reports a schematic of the IS-1 operon for each knock-out strain generated, along with the deletion position within the amino acidic sequence. Most data presented here concern the COH1 deletion strains, in which the expression of each of the antigens is higher by DNA microarray analysis (data not shown) as well as detectable by FACS analysis (see FIGURE 8). The double mutant in 2603 Δ80, Δ104 double mutant was constructed by sequential allelic exchanges of the shown alleles.

Immunization protocol

Immune sera for FACS experiments were obtained as follows.

Groups of 4 CD-1 outbred female mice 6-7 weeks old (Charles River Laboratories, Calco Italy) were immunized with the selected GBS antigens, (20 μg of each recombinant GBS antigen), suspended in 100 μl of PBS. Each group received 3 doses at days 0, 21 and 35. Immunization was performed through intra-peritoneal injection of the protein with an equal volume of Complete Freund's Adjuvant (CFA) for the first dose and Incomplete Freund's Adjuvant (IFA) for the following two doses. In each immunization scheme negative and positive control groups are used. Immune response was monitored by using serum samples taken on day 0 and 49.

FACS analysis

Preparation of paraformaldehyde treated GBS cells and their FACS analysis were carried out as follows.

GBS serotype COH1 strain cells were grown in Todd Hewitt Broth (THB; Difco Laboratories, Detroit, Mich.) to OD600nm = 0.5. The culture was centrifuged for 20 minutes at 5000 rpm and bacteria were washed once with PBS, resuspended in PBS containing 0.05% paraformaldehyde, and incubated for 1 hours at 37 °C and then overnight at 4°C. 50μl of fixed bacteria (OD600 0.1) were washed once with PBS, resuspended in 20μl of Newborn Calf Serum, (Sigma) and incubated for 20 min. at room temperature. The cells were then incubated for 1 hour at 4°C in 100μl of preimmune or immune sera, diluted 1:200 in dilution buffer (PBS, 20% Newborn Calf Serum, 0.1% BSA). After centrifugation and washing with 200μl of washing buffer (0.1% BSA in PBS), samples were incubated for 1 hour at 4°C with 50μl of R-Phicoerytrin conjugated F(ab)2 goat anti-mouse IgG (Jackson ImmunoResearch Laboratories; Inc.), diluted 1:100 in dilution buffer. Cells were washed with 200μl of washing buffer and resuspended in 200μl of PBS. Samples were analysed using a FACS Calibur apparatus (Becton Dickinson, Mountain View, Calf.) and data were analyzed using the Cell Quest Software (Becton Dickinson). A shift in mean fluorescence intensity of > 75 channels compared to preimmune sera from the same mice was considered positive. This cutoff

was determined from the mean plus two standard deviations of shifts obtained with control sera raised against mock purified recombinant proteins from cultures of *E. coli* carrying the empty expression vector and included in every experiment. Artifacts due to bacterial lysis were excluded using antisera raised against 6 different known cytoplasmic proteins all of which were negative

FACS data on COH1 single KO mutants for GBS 104 and GBS 80 indicated that GBS 80 is required for surface localization of GBS 104.

As shown in FIGURE 8, GBS 104 is not surface exposed in the Δ80 strain (second column, bottom), but is present in the whole protein extracts (see FIGURE 10). Mean shift values suggest that GBS 104 is partially responsible for GBS 80 surface exposure (Mean shift of GBS 80 is reduced to ~60% wild-type levels in Δ104), and that GBS 80 is over-expressed in the complemented strain (mean shift value ~200% wild-type level). The Δ80/pGBS 80 strain contains the GBS 80 orf cloned in the shuttle-vector pAM401 (Wirth, R., F. Y. An, et al. (1986). J Bacteriol 165(3): 831-6). The vector alone does not alter the secretion pattern of GBS 104 (right column). FACS was performed on mid-log fixed bacteria with mouse polyclonal antibodies as indicated at left. Black peak is pre-immune sera, colored peaks are sera from immunized animals.

EXAMPLE 3: Deletion of GBS 80 causes attenuation *in vivo*.

This example demonstrates that deletion of GBS 80 causes attenuation *in vivo*, suggesting that this protein contributes to bacterial virulence.

By using a mouse animal model, we studied the role of GBS 80 and GBS 104 in the virulence of S. agalactiae.

Groups of ten outbred female mice 5-6 week weeks old (Charles River Laboratories, Calco Italy) were inoculated intraperitoneally with different dilutions of the mutant strains and LD50 (lethal dose 50) were calculated according to the method of Reed and Muench [Reed, L. J. and H. Muench (1938).The American Journal of Hygiene 27(3): 493-7]. As presented in the table below the number of colony forming units (cfu) counted for both the Δ80 and the Δ80, Δ104 double mutants is about 10 fold higher when compared to the wild type strain suggesting that inactivation of GBS 80 but not GBS 104 is responsible for an attenuation in virulence. This finding indicates that GBS 80 gene in the AI-1 might contribute to virulence.

Table Lethal dose 50% analysis of AI-1 mutants in the 2603 strain background. LD50s were performed by IP injection of female CD1 mice at an age of 5-6 weeks. LD50s were calculated by the method of Reed and Muench (8).

GBS strain	LD_{50}, cfu	Number of Experiments
Wild Type 2603	2×10^8	4
Δ104 mutant	$\sim 2 \times 10^8$	1
Δ80 mutant	2.6×10^9	3
Δ80, Δ104 double mutant	$\sim 2 \times 10^9$	1

EXAMPLE 4: Effect of Adhesin Island Sortase Deletions on Surface Antigen Presentation

This example demonstrates the effect of adhesin island sortase deletions on surface antigen presentation.

FACS analysis results set forth in FIGURE 9 show that a deletion in sortase SAG0648 prevented GBS 104 from reaching the surface and slightly reduced the surface exposure of GBS 80 (fourth panel; mean shift value ~60% wild-type COH1). In the double sortase knock-out strain, neither antigen was surface exposed (far right panel). Either sortase alone was sufficient for GBS 80 to arrive at the bacterial surface (third and fourth columns, top). No effect was seen on surface exposure of antigens GBS 80 or GBS 104 in the ΔGBS 52 strain. Antibodies derived from purified GBS 52 were either non-specific or were FACS negative for GBS 52 (data not shown). FACS analysis was performed as described above (see EXAMPLE 2).

As shown in FIGURE 10, inactivation of GBS 80 has no effect on GBS 104 expression as much as GBS 104 knock out doesn't change the total amount GBS 80 expressed. The Western blot of whole protein extracts (strains noted above lanes) probed with anti-GBS 80 antisera is shown in panel A. Arrow indicates expected size of GBS 80 (60 kDa). GBS 80 antibodies recognize a doublet, the lower band is not present in ΔGBS 80 strains. Panel B shows a Western blot of whole protein extracts probed with anti-GBS 104 antisera. Arrow indicates expected size of GBS 104 (99.4 kDa). Protein extracts were prepared from the same bacterial cultures used for FACS (FIGURES 8 and 9). In conclusion, although GBS 104 does not arrive at the surface in the Δ80 strain by FACS (FIGURE 8, second column), it is present at approximately wild-type levels in the whole protein preps (B, second lane). Approximately 20 μg of each protein extract was loaded per lane.

Western-blot analysis

Aliquots of total protein extract mixed with SDS loading buffer (1x: 60 mM TRIS-HCl pH 6.8, 5% w/v SDS, 10% v/v glycerin, 0.1% Bromophenol Blue, 100 mM DTT) and boiled 5 minutes at 95° C, were loaded on a 12.5% SDS-PAGE precast gel (Biorad). The gel is run using a SDS-PAGE running buffer containing 250 mM TRIS, 2.5 mM Glycine and 0.1 %SDS. The gel is electroblotted onto nitrocellulose membrane at 200 mA for 60 minutes. The membrane is blocked for 60 minutes with PBS/0.05 % Tween-20 (Sigma), 10% skimmed milk powder and incubated O/N at 4° C with PBS/0.05 % Tween 20, 1% skimmed milk powder, with the appropriate dilution of the sera. After washing twice with PBS/0.05 % Tween, the membrane is incubated for 2 hours with peroxidase-conjugated secondary anti-mouse antibody (Amersham) diluted 1:4000. The nitrocellulose is washed three times for 10 minutes with PBS/0.05 % Tween and once with PBS and thereafter developed by Opti-4CN Substrate Kit (Biorad).

Example 5: Binding of Adhesin Island proteins to epithelial cells and effect of Adhesin Island proteins on capacity of GBS to adhere to epithelial cells.

This example illustrates the binding of AI proteins to epithelial cells and the effect of AI proteins on the capacity of GBS to adhere to epithelial cells.

Applicants analysed whether recombinant AI surface proteins GBS 80 or GBS 104 would demonstrate binding to various epithelial cells in a FACS analysis. Applicants also analysed whether

deletion of AI surface proteins GBS 80 or GBS 104 would effect the capacity of GBS to adhere to and invade ME180 cervical epithelial cells.

As shown in Figure 28, deletion of GBS 80 sequence from GBS strain isolate 2603 (serotype V) did not affect the capacity of the mutated GBS to adhere to and invade ME180 cervical epithelial cells. Here ME180 cervical carcinoma epithelial cells were infected with wild type GBS 2603 or GBS 2603 Δ80 isogenic mutant. After two hours of infection, non-adherent bacteria were washed off and infection prolonged for a further two hours and four hours. In invasion experiments, after each time point, was followed by a two hour antibiotic treatment. Cells were then lysed with 1% saponin and lysates platedon TSA plates. As shown in Figure 28, there was little difference between the percent invasion or percent adhesion of wild type and mutant strains up to the four hour time point.

Figure 30 repeats this experiment with both Δ104 and Δ 80 mutants from a different strain isolate. Here, ME180 cervical carcinoma epithelial cells were infected with GBS strain isolate COH (serotype III) wild type or COH1 ΔGBS 104 or COH1 Δ80 isogenic mutant. After one hour of infection, non-adherent bacteria were washed off and the cells were lysed with 1% saponin. The lysates were plated on TSA plates. As shown in Figure 30, while there was little difference in the percent invasion, there was a significant decrease in the percent association of the Δ104 mutant compared to both the wild type and Δ80 mutant.

The affect of AI surface proteins on the ability of GBS to translocate through an epithelial monolayer was also analysed. As shown in Figure 31, a GBS 80 knockout mutant strain partially loses the ability to translocate through an epithelial monolayer. Here epithelial monolayers were inoculated with wildtype or knockout mutant in the apical chamber of a transwell system for two hours and then non-adherent bacteria were washed off. Infection was prolonged for a further two and four hours. Samples were taken from the media of the basolateral side and the number of colony forming unties measured. Transepithelial electrical resistance measured prior to and after infection gave comparable values, indicating the maintenance of the integrity of the monolayer. By the six hour time point, the Δ80 mutants demonstrated a reduced percent transcytosis.

A similar experiment was conducted with GBS 104 knock out mutants. Here, as shown in Figure 22, the Δ104 mutants also demonstrated a reduced percent transcytosis, indicating that the mutant strains translocate through an epithelial monolayer less efficiently than their isogenic wild type counterparts.

Applicants also studied the effect of AI proteins on the capacity of a GBS strain to invade J774 macrophage-like cells. Here, J774 cells were infected with GBS COH1 wild type or COH1 ΔGBS104 or COH1 ΔGBS80 isogenic mutants. After one hour of infection, non-adherent bacteria were washed off and intracellular bacteria were recovered at two, four and six hours post antibiotic treatment. At each time point, cells were lysed with 0.25% Triton X-100 and lysates plated on TSA plates. As shown in Figure 32, the Δ104 mutant demonstrated a significantly reduced percent invasion compared to both the wild type and Δ80 mutant.

Example 6: Hyperoligomeric structures comprising AI surface proteins GBS 80 and GBS 104.

This example illustrates hyperoligomeric structures comprising AI surface proteins GBS 80 and GBS 104. A GBS isolate COH1 (serotype III) was adapted to increase expression of GBS 80. Figure 34 presents a regular negative stain electron micrograph of this mutant; no pilus or hyperoligomeric structures are distinguishable on the surface of the bacteria. When the EM stain is based on anti-GBS 80 antibodies labelled with 10 or 20 nm gold particles, the presence of GBS 80 throughout the hyperoligomeric structure is clearly indicated (Figures 36, 37 and 38). EM staining against GBS 104 (anti-GBS 104 antibodies labelled with 10 nm gold particles) also reveals the presence of GBS 104 primarily on or near the surface of the bacteria or potentially associated with bacterial peptidoglycans (Figure 39). Analysis of this same strain (over-expressing GBS 80) with a combination of both anti-GBS 80 (using 20 nm gold particles) and anti-GBS 104 (using 10 nm gold particles) reveals the presence of GBS 104 on the surface and within the hyperoligomeric structures (see Figures 40 and 41).

Example 7: GBS 80 is necessary for polymer formation and GBS 104 and sortase SAG0648 are necessary for efficient pili assembly

This example demonstrates that GBS 80 is necessary for formation of polymers and that GBS 104 and sortase SAG0648 are necessary for efficient pili assembly. GBS 80 and GBS 104 polymeric assembly was systematically analyzed in Coh1 strain single knock out mutants of each of the relevant coding genes in AI-1 (GBS 80, GBS 104, GBS 52, sag0647, and sag0648). Figure 41 provides Western blots of total protein extracts (strains noted above lanes) probed with either anti-GBS 80 (left panel) sera or anti-GBS 104 sera (right panel) for each of these Coh1 and Coh1 knock out strains. (Coh1, wild type Coh1; Δ80, Coh1 with GBS 80 knocked out; Δ104, Coh1 with GBS 104 knocked out; Δ52, Coh1 with GBS 52 knocked out; Δ647, Coh1 with SAG0647 knocked out; Δ648, Coh1 with SAG0648 knocked out, Δ647-8, Coh1 with SAG0647 and SAG0648 knocked out; Δ80/pGBS80, Coh1 with GBS 80 knocked out but complemented with a high copy number plasmid expressing GBS 80. Asterisks identify the monomer of GBS 80 and GBS 104.)

The smear of immunoreactive material observed in the wild type strain, along with its disappearance in Δ80 and Δ104 mutants, is consistent with the notion that such high molecular weight structures are composed of covalently linked (SDS-resistant) GBS 80 and GBS 104 subunits. The immunoblotting with both anti-GBS 80 (α-GBS 80) and anti-GBS 104 (α-GBS 104) revealed that deletion of sortase SAG0648 also interferes with the assembly of high molecular weight species, whereas the knock out mutant of the second sortase (SAG0647), even if somehow reduced, still maintains the ability to form polymeric structures.

Total extracts form GBS were prepared as follows. Bacteria were grown in 50 ml of Todd-Hewitt broth (Difco) to an OD_{600nm} of 0.5-0.6 and successively pelleted. After two washes in PBS the pellet was resuspended and incubated 3 hours at 37°C with mutanolisin. Cells were then lysed with at

least three freezing-thawing cycles in dry ice and a 37°C bath. The lysate was then centrifuged to eliminate the cellular debris and the supernatant was quantified. Approximately 40 μg of each protein extract was separated on SDS-PAGE. The gel was then subjected to immunoblotting with mice antisera and detected with chemiluminescence.

Example 8: GBS 80 is polymerized by an AI-2 sortase

This example illustrates that GBS 80 can be polymerized not only by AI-1 sortases, but also by AI-2 sortases. Figure 42 shows total cell extract immunoblots of GBS 515 strain, which lacks AI-1. The left panel, where an anti-GBS 67 sera was used, shows that GBS 67 from AI-2 is assembled into high-molecular weight-complexes, suggesting the formation of a second type of pilus. The same high molecular structure is observed when GBS 80 is highly expressed by reintroducing the gene within a plasmid (pGBS 80). By using anti-GBS 80 (right panel) sera on the same extracts, again it is observed that, with GBS 80 over expression (515/pGBS 80), a high-molecular weight structure is assembled. This implies that, in the absence of AI-1 sortases, AI-2 sortases (SAG1405 and SAG1406) can complement the lacking function, still being able to assemble GBS 80 in a pilus structure.

Example 9: Coh1 produces a high molecular weight molecule, the GBS 80 pilin

This example illustrates that Coh1 produces a high molecular weight molecule, greater than 1000 kDa, which is the GBS 80 pilin. Figure 43 provides silver-stained electrophoretic gels that show that Coh1 produces two macromolecules. One of these macromolecules disappears in the Coh1 GBS 80 knock out cells, but does not disappear in the Coh1 GBS 52 knock out mutant cells. The last two lanes on the right were loaded with 15 times the amount loaded in the other lanes. This was done in order to be able to count the bands. By doing this, a conservative size estimate of the top bands was calculated by starting at 240 kDa and considering each of 14 higher bands as the result of consecutive additions of a GBS 80 monomer.

Coh1, wild type Coh1; Δ80, Coh1 cells with GBS 80 knocked out; Δ52, Coh1 cells with GBS 52 knocked out; Δ80/pGBS 80, Coh1 cells with GBS 80 knocked out and complemented with a high copy number construct expressing GBS 80.

Example 10. GBS 52 is a minor component of the GBS pilus

This example illustrates that GBS 52 is present in the GBS pilus and is a minor component of the pilus. Figure 45 shows an immunoblot of total cell extracts from a GBS Coh1 strain and a GBS Coh1 strain knocked out for GBS 52 (Δ52). The total cell extracts were immunoblotted anti-GBS 80 antisera (left) and anti-GBS 52 antisera (right). Immunoblotting was performed using a 3-8% Tris-acetate polyacrylamide gel (Invitrogen) which provided excellent separation of large molecular weight proteins (see figure 41). When the gel was incubated with anti-GBS 80 sera, the bands from the Coh1 wild-type strain appeared shifted when compared to the Δ52 mutant. This observation

indicated a different size of the pilus polymeric components in the two strains. When the same gel was stripped and incubated with anti-GBS 52 sera the high-molecular subunits in the Coh1 wild-type strain showed similar molecular size of those in the correspondent lane in the left panel. These findings confirmed that GBS 52 is indeed associated with GBS 80 macro-molecular structures but represents a minor component of the GBS pilus.

Example 11: Pilus structures are present in the supernatant of GBS bacterial cultures

This example illustrates that the pilus structure assembled in Coh1 GBS is present in the supernatant of a bacterial cell culture. Figure 46 shows an immunoblot where the protein extract of the supernatant from cultures of different GBS mutant strains (117 = Coh1 GBS 80 knockout; 159= Coh1 GBS 104 knockout; 202= Coh1 GBS 52 knockout; 206= Coh1 GBS sag0647 knockout; 208= Coh1 GBS sag0648 knockout; 197= Coh1 GBS sag0647/sag0648 knockout; 179= Coh1 GBS 80 knockout complemented with a high copy plasmid expressing GBS 80). GBS 80 antisera detects the presence of pilus structures in the appropriate Coh1 strains.

The protein extract was prepared as follows. Bacteria were grown in THB to an OD_{600nm} of 0.5-0.6 and the supernatant was separated from the cells by centrifugation. The supernatant was then filtered (∅ 0.2 μm) and 1 ml was added with 60% TCA for protein precipitation.
GBS pili were also extracted from the fraction of surface-exposed proteins in Coh1 strain and its GBS 80 knock out mutant as described hereafter. Bacteria were grown to an OD_{600nm} of 0.6 in 50 ml of THB at 37°C. Cells were washed once with PBS and the pellet was then resuspended in 0.1 M KPO4 pH 6.2, 40% sucrose, 10 mM MgCl2, 400U/ml mutanolysin and incubated 3 hours at 37°C. Protoplasts were separated by centrifugation and the supernatant was recovered and its protein content measured.

In order to study the dynamics of pilus production during different growth phases, 1 ml supernatant of a culture at different OD_{600nm} was TCA precipitated and loaded onto a 3-8% SDS-PAGE as described before. Figure 47 shows the corresponding Western blot with GBS 80 anti-sera. The first group of lanes (left five sample lanes) refer to a Coh1 strain growth (OD_{600nm} are noted above the lanes) whereas the second group of lanes (right five samples) are from a GBS 80 knock out strain over expressing GBS 80. The experiment shows that pilus macromolecular structures can be found in the supernatant in all of the growth phases tested.

Example 12: In GBS strain Coh1, only GBS 80 and a sortase (sag0647 or sag0648) is required for polymerization

This example describes requirements for pilus formation in Coh1. Figure 48 shows a Western blot of total protein extracts (prepared as described before) using anti-GBS 80 sera on Coh1 clones. (Coh1, wild type Coh1; Δ104, Coh1 knocked out for GBS 104, Δ647, Coh1 knocked out for sag0647, Δ648, Coh1 knocked for sag0648, Δ647-8, Coh1 knocked out for sag0647 and sag0648; 515, wild

type bacterial strain 515, which lacks an AI-1; p80 a high copy number plasmid which expresses GBS 80.) The data show that only the double sortase mutant is unable to polymerize GBS 80 indicating that the '*conditio sine qua non*' for pilus polymerization is the co-existence of GBS 80 with at least one sortase. This result leads to a reasonable assumption that SAG1405 and SAG1406 are responsible for polymerization in this strain.

Example 13: GBS 80 can be expressed in *L. lactis* under its own promoter and terminator sequences

This example demonstrates that *L. lactis*, a non-pathogenic bacterium, can express GBS AI polypeptides such as GBS 80. *L. lactis* M1363 (*J. Bacteriol. 154* (1983):1-9) was transformed with a construct encoding GBS 80. Briefly, the construct was prepared by cloning a DNA fragment containing the gene coding for GBS 80 under its own promoter and terminator sequences into plasmid pAM401 (a shuttle vector for *E. coli* and other Gram positive bacteria; *J. Bacteriol. 163* (1986):831-836). Total extracts of the transformed bacteria in log phase were separated on SDS-PAGE, transferred to membranes, and incubated with antiserum against GBS 80. A polypeptide corresponding to the molecular weight of GBS 80 was detected in the lanes containing total extracts of *L. lactis* transformed with the GBS 80 construct. See Figures 133A and 133B, lanes 6 and 7. This same polypeptide was not detected in the lane containing total extracts of *L. lactis* not transformed with the GBS 80 construct, lane 9. This example shows that *L. lactis* can express GBS 80 under its own promoter and terminator.

Example 14: *L. lactis* modified to express GBS AI-1 under the GBS 80 promoter and terminator sequences expresses GBS 80 in polymeric structures

This example demonstrates the ability of *L. lactis* to express GBS AI-1 polypeptides and to incorporate at least some of the polypeptides into oligomers. *L. lactis* was transformed with a construct containing the genes encoding GBS AI-1 polypeptides. Briefly, the construct was prepared by cloning a DNA fragment containing the genes for GBS 80, GBS 52, SAG0647, SAG0648, and GBS 104 under the GBS 80 promoter and terminator sequences into construct pAM401. The construct was transformed into *L. lactis* M1363. Total extracts of log phase transformed bacteria were separated on reducing SDS-PAGE, transferred to membranes, and incubated with antiserum against GBS 80. A polypeptide with a molecular weight corresponding to the molecular weight of GBS 80 was detected in the lanes containing *L. lactis* transformed with the GBS AI-1 encoding construct. See Figure 134, lane 2. In addition, the same lane also showed immunoreactivity of polypeptides having higher molecular weights than the polypeptide having the molecular weight of GBS 80. These higher molecular weight polypeptides are likely oligomers of GBS 80. Oligomers of similar molecular

weights were also observed on a Western blot of the culture supernatant of the transformed *L. lactis*. See lane 4 of Figure 135. Thus, this example shows that *L. lactis* transformed to express GBS AI-1 can efficiently polymerize GBS 80 in the form of a pilus. This pilus structure can likely be purified from either the cell culture supernatant or cell extracts.

Example 15: Cloning and Expression of *S. pneumoniae* Sp0462

This example describes the production of a clone encoding a Sp0462 polypeptide and expression of the clone. To produce a clone encoding Sp0462, the open reading frame encoding Sp0462 was amplified using primers that annealed within the full-length Sp0462 open reading frame sequence. Figure 150A provides a 893 amino acid sequence of Sp0462. The primers used to produce a clone encoding the Sp0462 polypeptide are shown in Figure 150B. These primers annealed to the nucleotide sequences encoding the amino acid residues indicated by underlining in Figure 150A. Amplification of the open reading frame encoding Sp0462 using these primers produced the amplicon shown at lane 2 of the agarose gel provided in Figure 160. The Sp0462 clone encodes amino acid residues 38-862 of the 893 amino acid residue Sp0462 protein; the italicized residues in Figure 150A were eliminated. Figure 151A provides a schematic depiction of the recombinant Sp0462 polypeptide. Figure 151B shows a schematic depiction of the full-length Sp0462 polypeptide. Both the recombinant Sp0462 encoded by the clone and the full-length Sp0462 protein have two collagen binding protein type B (Cna B) domains and a von Hillebrand factor A (vWA) domain. The cloned recombinant Sp0462 lacks the LPXTG motif present in the full-length Sp0462 protein. Western blot analysis for expression of the Sp0462 clone did not result in detection of polypeptides with serum obtained from *S. pneumoniae*–infected patients (Figure 152A) or GBS 80 antiserum (Figure 152B).

Example 16: Cloning and Expression of *S. pneumoniae* Sp0463

This example describes the production of a clone encoding a Sp0463 polypeptide and detection of recombinant Sp0463 polypeptide expressed from the clone. To produce a clone encoding Sp0463, the open reading frame encoding Sp0463 was amplified using primers that annealed within the full-length Sp0463 open reading frame sequence. Figure 153A provides a 665 amino acid sequence of Sp0463. The primers used to produce the clone encoding Sp0463 polypeptide are shown in Figure 153B. These primers annealed to the nucleotide sequences encoding the amino acid residues indicated by underlining in Figure 153A. Amplification of the open reading frame encoding Sp0463 using these primers produced the amplicon shown at lane 3 of the agarose gel provided in Figure 160. The Sp0463 clone encodes amino acid residues 23-627 of the 665 amino acid residue Sp0463 protein; the italicized residues in Figure 153A were eliminated. Figure 154A provides a schematic depiction of the recombinant Sp0463 polypeptide. Figure 154B shows a schematic depiction of the full-length Sp0463 polypeptide. Both the recombinant Sp0463 encoded by the clone and the full-length Sp0463 protein have a Cna B domain and an E box motif. The cloned recombinant

Sp0463 lacks the LPXTG motif present in the full-length Sp0463 protein. Expression of the Sp0463 clone resulted in the detection of a 60 kD polypeptide, the expected molecular weight of the recombinant Sp0463 polypeptide, by Western blot analysis. See Figure 155.

Example 17: Cloning and Expression of *S. pneumoniae* Sp0464

This example describes the production of a clone encoding a Sp0464 polypeptide and detection of recombinant Sp0464 polypeptide expressed from the clone. To produce a clone encoding Sp0464, the open reading frame encoding Sp0464 was amplified using primers that annealed either within the full-length Sp0464 open reading frame sequence. Figure 157A provides a 393 amino acid sequence of Sp0464. The primers used to produce a clone encoding the Sp0464 polypeptide are shown in Figure 157B. These primers annealed to the nucleotide sequences encoding the amino acid residues indicated by underlining in Figure 157A. Amplification of the open reading frame encoding Sp0464 using these primers produced the amplicon shown at lane 4 of the agarose gel provided in Figure 160. The Sp0464 clone encodes amino acid residues 19-356 of the 393 amino acid residue Sp0464 protein; the italicized residues in Figure 157A were eliminated. Figure 158A provides a schematic depiction of the recombinant Sp0464 polypeptide. Figure 158B shows a schematic depiction of the full-length Sp0464 polypeptide. Both the recombinant Sp0464 encoded by the clone and the full-length Sp0464 protein have two Cna B domains. The cloned recombinant Sp0464 lacks the LPXTG motif present in the full-length Sp0464 protein. Expression of the Sp0464 clone resulted in the detection of a 38 kD polypeptide, the expected molecular weight of the recombinant Sp0464 polypeptide, by Western blot analysis. See Figure 159.

Example 18: Intranasal Immunization of Mice with Recombinant *L. lactis* Expressing GBS 80 and Subsequent Challenge

This example describes a method of intranasally immunizing mice using *L. lactis* that express GBS 80. Intranasal immunization consisted of 3 doses at days 0, 14 and 28, each dose administered in three consecutive days. Each day, groups of 3 CD-1 outbred female mice 6-7 weeks old (Charles River Laboratories, Calco Italy) were immunized intranasally with 10^9 or 10^{10} CFU of the recombinant *Lactococcus lactis* suspended in 20 µl of PBS. In each immunization scheme negative (wild-type *L. lactis*) and positive (recombinant GBS80) control groups were used. The immune response of the dams was monitored by using serum samples taken on day 0 and 49. The female mice were bred 2-7 days after the last immunization (at approximately t= 36 – 37), and typically had a gestation period of 21 days. Within 48 hours of birth, the pups were challenged via I.P. with GBS in a dose approximately equal to an amount which would be sufficient to kill 90 % of immunized pups (as determined by empirical data gathered from PBS control groups). The GBS challenge dose is preferably administered in 50ml of THB medium. Preferably, the pup challenge takes place at 56 to 61 days after the first immunization. The challenge inocula were prepared starting from frozen

cultures diluted to the appropriate concentration with THB prior to use. Survival of pups was monitored for 5 days after challenge.

Example 19: Subcutaneous Immunization of Mice with Recombinant *L. lactis* Expressing GBS 80 and Subsequent Challenge

This example describes a method of subcutaneous immunization mice using *L. lactis* that express GBS 80. Subcutaneous immunization consists of 3 doses at days 0, 14 and 28. Groups of 3 CD-1 outbred female mice 6-7 weeks old (Charles River Laboratories, Calco Italy) were injected subcutaneously with 10^9 or 10^{10} CFU of the recombinant *Lactococcus lactis* suspended in 100 µl of PBS. In each immunization scheme, negative (wild-type *L. lactis*) and positive (recombinant GBS80) control groups were used. The immune response of the dams was monitored by using serum samples taken on day 0 and 49. The female mice were bred 2-7 days after the last immunization (at approximately t= 36 – 37), and typically had a gestation period of 21 days. Within 48 hours of birth, the pups were challenged via I.P. with GBS in a dose approximately equal to an amount which would be sufficient to kill 90 % of immunized pups (as determined by empirical data gathered from PBS control groups). The GBS challenge dose is preferably administered in 50ml of THB medium. Preferably, the pup challenge takes place at 56 to 61 days after the first immunization. The challenge inocula were prepared starting from frozen cultures diluted to the appropriate concentration with THB prior to use. Survival of pups was monitored for 5 days after challenge.

Example 20: Immunization of Mice with GAS AI polypeptides and Subsequent Intranasal Challenge

This example describes a method of immunizing mice with GAS AI polypeptides and subsequently intranasally challenging the mice with GAS bacteria. Groups of 10 CD1 female mice aged between 6 and 7 weeks are immunized with a combination of GAS antigens of the invention GAS 15, GAS 16, and GAS 18, (15 µg of each recombinant antigen, derived from M1 strain SF370) or *L. lactis* expressing the M1 strain SF370 adhesin island, suspended in 100 µl of suitable solution. Each group receives 3 doses at days 0, 21 and 45. Immunization is performed through subcutaneous or intraperitoneal injection for the GAS 15, GAS 16, GAS 18 protein combination. The protein combination is administered with an equal volume of Complete Freund's Adjuvant (CFA) for the first dose and Incomplete Freund's Adjuvant (IFA) for the following two doses. Immunization is performed intranasally for the *L. lactis* expressing the M1 strain SF370 adhesin island. In each immunization scheme negative and positive control groups are used.

The negative control group for the mice immunized with the GAS 15, GAS 16, GAS 18 protein combination included mice immunized with PBS. The negative control group for the mice immunized with *L. lactis* expressing the M1 strain SF370 adhesin island, included mice immunized

with either wildtype *L. lactis* or *L. lactis* transformed with the pAM401 expression vector lacking any cloned adhesin island sequence.

The positive control groups included mice immunized with purified M1 strain SF370 M protein.

Immunized mice are then anaesthetized with Zoletil and challenged intranasally with a 25 μL suspension containing 1.2×10^6 or 1.2×10^8 CFU of ISS 3348 in THB. Animals are observed daily and checked for survival.

Example 21: Active Maternal Immunization Assay

As used herein, an Active Maternal Immunization assay refers to an *in vivo* protection assay where female mice are immunized with the test antigen composition. The female mice are then bred and their pups are challenged with a lethal dose of GBS. Serum titers of the female mice during the immunization schedule are measured as well as the survival time of the pups after challenge.

Mouse immunization

Specifically, groups of 4 CD-1 outbred female mice 6-8 weeks old (Charles River Laboratories, Calco Italy) are immunized with one or more GBS antigens, (20 μg of each recombinant GBS antigen), suspended in 100 μl of PBS. Each group receives 3 doses at days 0, 21 and 35. Immunization is performed through intra-peritoneal injection of the protein with an equal volume of Complete Freund's Adjuvant (CFA) for the first dose and Incomplete Freund's Adjuvant (IFA) for the following two doses. In each immunization scheme negative and positive control groups are used.

Immune response is monitored by using serum samples taken on day 0 and 49. The sera are analyzed as pools from each group of mice.

Active maternal immunization

A maternal immunization/neonatal pup challenge model of GBS infection was used to verify the protective efficacy of the antigens in mice. The mouse protection study was adapted from Rodewald et al. (Rodewald et al. J. Infect. Diseases 166, 635 (1992)). In brief, CD-1 female mice (6-8 weeks old) were immunized before breeding, as described above. The mice received 20 μg of protein per dose when immunized with a single antigen and 60 μg of protein per dose (15 μg of each antigen) when immunized with the combination of antigens. Mice were bred 2-7 days after the last immunization. Within 48 h of birth, pups were injected intraperitoneally with 50 μl of GBS culture. Challenge inocula were prepared starting from frozen cultures diluted to the appropriate concentration with THB before use. In preliminary experiments (not shown), the challenge doses per pup for each strain tested were determined to cause 90% lethality. Survival of pups was monitored for 2 days after challenge. Protection was calculated as (percentage

deadControl minus percentage deadVaccine) divided by percentage deadControl multiplied by 100. Data were evaluated for statistical significance by Fisher's exact test.

Embodiments of the Invention

The invention encompasses, but is not limited to, the embodiments enumerated below.

1. An immunogenic composition comprising a purified Group B Streptococcus (GBS) adhesin island (AI) polypeptide in oligomeric form.

2. The immunogenic composition of embodiment 1 wherein the GBS AI polypeptide is selected from a GBS AI-1.

3. The immunogenic composition of embodiment 1 wherein the GBS AI polypeptide is selected from a GBS AI-2.

1. An immunogenic composition comprising a purified Group B Streptococcus (GBS) adhesin island (AI) polypeptide in oligomeric form.

2. The immunogenic composition of embodiment 1 wherein the GBS AI polypeptide is selected from a GBS AI-1.

3. The immunogenic composition of embodiment 1 wherein the GBS AI polypeptide is selected from a GBS AI-2.

4. The immunogenic composition of any of embodiments 1-3 wherein the GBS AI polypeptide comprises a sortase substrate motif.

5. The immunogenic composition of embodiment 4 wherein the sortase substrate motif is an LPXTG motif.

6. The immunogenic composition of embodiment 5 wherein the LPXTG motif is represented by the amino acid sequence XPXTG, wherein the X at amino acid position 1 is an L, an I, or an F and the X at amino acid position 3 is any amino acid residue.

7. The immunogenic composition of any one of embodiments 1-3 wherein the GBS AI polypeptide affects the ability of GBS bacteria to adhere to epithelial cells.

8. The immunogenic composition of any one of embodiments 1-3 wherein the GBS AI polypeptide affects the ability of GBS bacteria to invade epithelial cells.

9. The immunogenic composition of any one of embodiments 1-3 wherein the GBS AI polypeptide affects the ability of GBS bacteria to translocate through an epithelial cell layer.

10. The immunogenic composition of any one of embodiments 1-3 wherein the GBS AI polypeptide is capable of associating with an epithelial cell surface.

11. The immunogenic composition of embodiment 10 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

12. The immunogenic composition of any of embodiments 1-3 wherein the GBS AI polypeptide is a full-length GBS AI protein.

13. The immunogenic composition of any of embodiments 1-3 wherein the GBS AI polypeptide is a fragment of a full-length GBS AI protein.

14. The immunogenic composition of embodiment 13 wherein the fragment comprises at least 7 contiguous amino acid residues of the GBS AI protein.

15. The immunogenic composition of embodiment 2 wherein the GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.

16. The immunogenic composition of embodiment 3 wherein the GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof.

17. The immunogenic composition of embodiment 15 wherein the GBS AI polypeptide is GBS 80.

18. The immunogenic composition of any of embodiments 1-3 or 15-17 wherein the oligomeric form is a hyperoligomer.

19. The immunogenic composition of any of embodiments 1-3, or 15-17 further comprising a Gram positive bacterium antigen not associated with an AI.

20. The immunogenic composition of embodiment 19 wherein the antigen is selected from the group consisting of GBS 322 and GBS 276.

21. The immunogenic composition of embodiment 20 wherein the antigen is GBS 322.

22. An immunogenic composition comprising a purified Gram positive bacteria adhesin island (AI) polypeptide in an oligomeric form.

23. The immunogenic composition of embodiment 22 wherein the Gram positive bacteria is of a genus selected from the group consisting of *Streptococcus*, *Enterococcus*, *Staphylococcus*, or *Listeria*.

24. The immunogenic composition of embodiment 23 wherein the Gram positive bacteria is of the genus *Streptococcus*.

25. The immunogenic composition of any of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide comprises a sortase substrate motif.

26. The immunogenic composition of embodiment 25 wherein the sortase substrate motif is an LPXTG motif.

27. The immunogenic composition of any one of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide affects the ability of Gram positive bacteria to adhere to epithelial cells.

28. The immunogenic composition of any one of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide affects the ability of Gram positive bacteria to invade epithelial cells.

29. The immunogenic composition of any one of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide affects the ability of Gram positive bacteria to translocate through an epithelial cell layer.

30. The immunogenic composition of any one of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide is capable of associating with an epithelial cell surface.

31. The immunogenic composition of embodiment 30 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

32. The immunogenic composition of any of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide is a full-length Gram positive bacteria AI protein.

33. The immunogenic composition of any of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide is a fragment of a full-length Gram positive bacteria AI protein.

34. The immunogenic composition of embodiment 33 wherein the fragment comprises at least 7 contiguous amino acid residues of the Gram positive bacteria AI protein.

35. The immunogenic composition of embodiment 24 wherein the genus *Streptococcus* bacteria is Group A Streptococcus (GAS) bacteria and the Gram positive bacteria AI polypeptide is a GAS AI polypeptide.

36. The immunogenic composition of embodiment 35 wherein the GAS AI polypeptide is selected from a GAS AI-1.

37. The immunogenic composition of embodiment 35 wherein the GAS AI polypeptide is selected from a GAS AI-2.

38. The immunogenic composition of embodiment 35 wherein the GAS AI polypeptide is selected from a GAS AI-3.

39. The immunogenic composition of embodiment 35 wherein the GAS AI polypeptide is selected from a GAS AI-4.

40. The immunogenic composition of any of embodiments 35-39 wherein the GAS AI polypeptide comprises a sortase substrate motif.

41. The immunogenic composition of embodiment 40 wherein the sortase substrate motif is an LPXTG motif.

42. The immunogenic composition of embodiment 41 wherein the LPXTG motif is represented by XXXXG, wherein the X at the first amino acid position is an L, a V, an E, or a Q, wherein the X at the second amino acid position is P if the X at the first amino acid position is an L, the X at the second amino acid position is a V if the X at the first amino acid position is an E or a Q, or the X at the second amino acid position is a V or a P if the X at the first amino acid position is a V, wherein the X at the third amino acid position is any amino acid residue, and wherein the X at the fourth amino acid position is a T if the X at the first amino acid position is a V, an E, or a Q, or the X at the fourth amino acid position is a T, an S, or an A if the X at the first amino acid position is an L.

43. The immunogenic composition of any one of embodiments 35-39 wherein the GAS AI polypeptide affects the ability of GAS bacteria to adhere to epithelial cells.

44. The immunogenic composition of any one of embodiments 35-39 wherein the GAS AI polypeptide affects the ability of GAS bacteria to invade epithelial cells.

45. The immunogenic composition of any one of embodiments 35-39 wherein the GAS AI polypeptide affects the ability of GAS bacteria to translocate through an epithelial cell layer.

46. The immunogenic composition of any one of embodiments 35-39 wherein the GAS AI polypeptide is capable of associating with an epithelial cell surface.

47. The immunogenic composition of embodiment 46 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

48. The immunogenic composition of any of embodiments 35-39 wherein the GAS AI polypeptide is a full-length GAS AI protein.

49. The immunogenic composition of any of embodiments 35-39 wherein the GAS AI polypeptide is a fragment of a full-length GAS AI protein.

50. The immunogenic composition of embodiment 49 wherein the fragment comprises at least 7 contiguous amino acid residues of the GAS AI protein.

51. The immunogenic composition of embodiment 36 wherein the GAS AI-1 polypeptide is selected from the group consisting of M6_Spy0157, M6_Spy0159, M6_Spy0160, CDC SS 410_fimbrial, ISS3650_fimbrial, DSM2071_fimbrial, and fragments thereof.

52. The immunogenic composition of embodiment 37 wherein the GAS AI-2 polypeptide is selected from the group consisting of GAS15, GAS16, GAS18, and fragments thereof.

53. The immunogenic composition of embodiment 38 wherein the GAS AI-3 polypeptide is selected from the group consisting of SpyM3_0098, SpyM3_0100, SpyM3_0102, SpyM3_0104, SPs0100, SPs0102, SPs0104, SPs0106, orf78, orf80, orf82, orf84, spyM18_0126, spyM18_0128, spyM18_0130, spyM18_0132, SpyoM01000156, SpyoM01000155, SpyoM01000154, SpyoM01000153, SpyoM01000152, SpyoM01000151, SpyoM01000150, SpyoM01000149, ISS3040_fimbrial, ISS3776_fimbrial, ISS4959_fimbrial, and fragments thereof.

53. The immunogenic composition of embodiment 39 wherein the GAS AI-4 polypeptide is selected from the group consisting of 19224134, 19224135, 19224137, 19224139, 19224141, 20010296_fimbrial, 20020069_fimbrial, CDC SS 635_fimbrial, ISS4883_fimbrial, ISS4538_fimbrial, and fragments thereof.

54. The immunogenic composition of embodiment 24 wherein the *Streptococcus* bacteria is *Streptococcus pneumoniae* and the Gram positive bacteria AI polypeptide is a *S. pneumoniae* AI polypeptide.

55. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide comprises a sortase substrate motif.

56. The immunogenic composition of embodiment 55 wherein the sortase substrate motif is an LPXTG motif.

57. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide affects the ability of *S. pneumoniae* to adhere to epithelial cells.

58. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide affects the ability of *S. pneumoniae* to invade epithelial cells.

59. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide affects the ability of *S. pneumoniae* to translocate through an epithelial cell layer.

60. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide is capable of associating with an epithelial cell surface.

61. The immunogenic composition of embodiment 60 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

62. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide is a full-length *S. pneumoniae* AI protein.

63. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide is a fragment of a full-length *S. pneumoniae* AI protein.

64. The immunogenic composition of embodiment 63 wherein the fragment comprises at least 7 contiguous amino acid residues of the *S. pneumoniae* AI protein.

65. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide is selected from the group consisting of SP0462, SP0463, SP0464, orf3_670, orf4_670, orf5_670, ORF3_14CSR, ORF4_14CSR, ORF5_14CSR, ORF3_19AH, ORF4_19AH, ORF5_19AH, ORF3_19FTW, ORF4_19FTW, ORF5_19FTW, ORF3_23FP, ORF4_23FP, ORF5_23FP, ORF3_23FTW, ORF4_23FTW, ORF5_23FTW, ORF3_6BF, ORF4_6BF, ORF5_6BF, ORF3_6BSP, ORF4_6BSP, ORF5_6BSP, ORF3_9VSP, ORF4_9VSP, ORF5_9VSP, and fragments thereof.

66. The immunogenic composition of any one of embodiments 22-24, 35-39, 51-54, or 65 wherein the oligomeric form is a hyperoligomer.

67. The immunogenic composition of any one of embodiments 22-24, 35-39, 51-54, or 65 further comprising a Gram positive bacteria antigen not associated with an AI.

68. The immunogenic composition of embodiment 67 wherein the antigen is selected from the group consisting of GBS 322 and GBS 276.

69. An immunogenic composition comprising a first and a second Group B Streptococcus (GBS) adhesin island (AI) polypeptide.

70. The immunogenic composition of embodiment 69 wherein a full-length polynucleotide sequence encoding for the first GBS AI polypeptide is not present in a GBS bacteria genome comprising a polynucleotide sequence encoding for the second GBS AI polypeptide.

71. The immunogenic composition of embodiment 69 wherein polynucleotides encoding the first and the second GBS AI polypeptide are each present in genomes of more than one GBS serotype and strain isolate.

72. The immunogenic composition of embodiment 69 wherein the first GBS AI polypeptide is encoded by a GBS AI-1.

73. The immunogenic composition of embodiment 69 wherein the first GBS AI polypeptide is encoded by a GBS AI-2.

74. The immunogenic composition of embodiment 72 wherein the second GBS AI polypeptide is encoded by a GBS AI-2.

75. The immunogenic composition of embodiment 73 wherein the second GBS AI polypeptide is encoded by a GBS AI-2.

76. The immunogenic composition of embodiment 72 wherein the second GBS AI polypeptide is encoded by a GBS AI-1.

77. The immunogenic composition of embodiment 73 wherein the second GBS AI polypeptide is encoded by a GBS AI-1.

78. The immunogenic composition of embodiment 72 wherein the first GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.

79. The immunogenic composition of embodiment 73 wherein the first GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof.

80. The immunogenic composition of embodiment 74 or 75 wherein the second GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof, and wherein the first and the second GBS AI polypeptide are not the same polypeptide.

81. The immunogenic composition of embodiment 76 or 77 wherein the second GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof, and wherein the first and the second GBS AI polypeptide are not the same polypeptide.

82. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide comprises a sortase substrate motif.

83. The immunogenic composition of embodiment 82 wherein the sortase substrate motif is an LPXTG motif.

84. The immunogenic composition of embodiment 83 wherein the LPXTG motif is represented by the sequence XPXTG, wherein the X at amino acid position 1 is an L, an I, or an F and the X at amino acid position 3 is any amino acid residue.

85. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide affects the ability of GBS bacteria to adhere to epithelial cells.

86. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide affects the ability of GBS bacteria to invade epithelial cells.

87. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide affects the ability of GBS bacteria to translocate through an epithelial cell layer.

88. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide is capable of associating with an epithelial cell surface.

89. The immunogenic composition of embodiment 88 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

90. The immunogenic composition of any of embodiments 69-77 wherein the first GBS AI polypeptide is a full-length GBS AI protein.

91. The immunogenic composition of any of embodiments 69-77 wherein the first GBS AI polypeptide is a fragment of a full-length GBS AI protein.

92. The immunogenic composition of embodiment 91 wherein the fragment comprises at least 7 contiguous amino acid residues of the first GBS AI protein.

93. The immunogenic composition of any one of embodiments 69-79 wherein the first GBS AI polypeptide is in oligomeric form.

94. The immunogenic composition of any one of embodiments 69-77 wherein the second GBS AI polypeptide is in oligomeric form.

95. The immunogenic composition of any one of embodiments 69-79 wherein the first and the second GBS AI polypeptide are associated in a single oligomeric form.

96. The immunogenic composition of embodiment 95 wherein the first and the second GBS AI polypeptides are chemically associated.

97. The immunogenic composition of embodiment 95 wherein the first and the second GBS AI polypeptides are physically associated.

98. The immunogenic composition of embodiment 93 wherein the oligomeric form is a hyperoligomer.

99. The immunogenic composition of embodiment 94 wherein the oligomeric form is a hyperoligomer.

100. The immunogenic composition of embodiment 76 wherein the first GBS AI polypeptide is GBS 80 and the second GBS AI polypeptide is GBS 104.

101. The immunogenic composition of embodiment 74 wherein the first GBS AI polypeptide is GBS 80 and the second GBS AI polypeptide is GBS 67.

102. The immunogenic composition of any one of embodiments 69-79, 100, or 101 further comprising a GBS polypeptide not associated with an AI.

103. The immunogenic composition of embodiment 102 wherein the GBS polypeptide not associated with an AI is selected from the group consisting of GBS 322 and GBS 276.

104. The immunogenic composition of embodiment 103 wherein the GBS polypeptide not associated with an AI is GBS 322.

105. An immunogenic composition comprising a first and a second Gram positive bacteria adhesin island (AI) polypeptide.

106. The immunogenic composition of embodiment 105 wherein a full length polynucleotide sequence encoding for the first Gram positive bacteria AI polypeptide is not present in a genome of a Gram positive bacteria comprising a full length polynucleotide sequence encoding for the second Gram positive bacteria AI polypeptide.

107. The immunogenic composition of embodiment 105 wherein polynucleotides encoding the first and the second Gram positive bacteria AI polypeptide are each present in genomes of more than one Gram positive bacteria serotype and strain isolate.

108. The immunogenic composition of embodiment 105 wherein the first and the second Gram positive bacteria AI polypeptides are of different Gram positive bacteria species.

109. The immunogenic composition of embodiment 105 wherein the first and the second Gram positive bacteria AI polypeptides are of the same Gram positive bacteria species.

110. The immunogenic composition of embodiment 105 wherein the first and the second Gram positive bacteria AI polypeptides are from different AI subtypes.

111. The immunogenic composition of embodiment 105 wherein the first and the second Gram positive bacteria AI polypeptides are from the same AI subtype.

112. The immunogenic composition of embodiment 105 wherein the first Gram positive bacteria AI polypeptide has detectable surface exposure on a first Gram positive bacteria strain or serotype but not a second Gram positive bacteria strain or subtype and the second Gram positive bacteria AI polypeptide has detectable surface exposure on the second Gram positive bacteria strain or serotype but not the first Gram positive bacteria strain or serotype.

113. The immunogenic composition of embodiment 105 wherein the Gram positive bacteria is *S. pneumonaie*, *S. mutans*, *E. faecalis*, *E. faecium*, *C. difficile*, *L. monocytogenes*, or *C. diphtheriae*.

114. The immunogenic composition of any of embodiments 105-113 wherein the first and the second Gram positive bacteria AI polypeptides comprise a sortase substrate motif.

115. The immunogenic composition of embodiment 114 wherein the sortase substrate motif is an LPXTG motif.

116. The immunogenic composition of embodiment 115 wherein the LPXTG motif is represented by XXXXG, wherein the X at amino acid position 1 is an L, a V, an E, an I, an F, or a Q, wherein X at amino acid position 2 is a P if X at amino acid position 1 is an L, an I, or an F, wherein X at amino acid position 2 is a V if X at amino acid position 1 is a E or a Q, wherein X at amino acid position 2 is a V or a P if X at amino acid position 1 is a V, wherein X at amino acid position 3 is any amino acid residue, wherein X at amino acid position 4 is a T if X at amino acid position 1 is a V, E, I, F, or Q, and wherein X at amino acid position 4 is a T, S, or A if X at amino acid position 1 is an L.

117. The immunogenic composition of embodiment 105 wherein the first Gram positive bacteria AI polypeptide is a first Group A Streptococcus (GAS) AI polypeptide.

118. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide comprises a sortase substrate motif.

119. The immunogenic composition of embodiment 118 wherein the sortase substrate motif is an LPXTG motif.

120. The immunogenic composition of embodiment 119 wherein the LPXTG motif is represented by XXXXG, wherein the X at the first amino acid position is an L, a V, an E, or a Q, wherein the X at the second amino acid position is P if the X at the first amino acid position is an L, the X at the second amino acid position is a V if the X at the first amino acid position is an E or a Q, or the X at the second amino acid position is a V or a P if the X at the first amino acid position is a V, wherein the X at the third amino acid position is any amino acid residue, and wherein the X at the fourth amino acid position is a T if the X at the first amino acid position is a V, an E, or a Q, or the X at the fourth amino acid position is a T, an S, or an A if the X at the first amino acid position is an L.

121. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide affects the ability of GAS bacteria to adhere to epithelial cells.

122. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide affects the ability of GAS bacteria to invade epithelial cells.

123. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide affects the ability of GAS bacteria to translocate through an epithelial cell layer.

124. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is capable of associating with an epithelial cell surface.

125. The immunogenic composition of embodiment 117 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

126. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a full-length GAS AI protein.

127. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a fragment of a full-length GAS AI protein.

128. The immunogenic composition of embodiment 127 wherein the fragment comprises at least 7 contiguous amino acid residues of the GAS AI protein.

129. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a first GAS AI-1 polypeptide.

130. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a first GAS AI-2 polypeptide.

131. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a first GAS AI-3 polypeptide.

132. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a first GAS AI-4 polypeptide.

133. The immunogenic composition of any one of embodiments 117 or 129-132 wherein the second Gram positive bacteria AI polypeptide is a second GAS AI polypeptide.

134. The immunogenic composition of embodiment 133 wherein the second GAS AI polypeptide is a second GAS AI-1 polypeptide.

135. The immunogenic composition of embodiment 133 wherein the second GAS AI polypeptide is a second GAS AI-2 polypeptide.

136. The immunogenic composition of embodiment 133 wherein the second GAS AI polypeptide is a second GAS AI-3 polypeptide.

137. The immunogenic composition of embodiment 133 wherein the second GAS AI polypeptide is a second GAS AI-4 polypeptide.

138. The immunogenic composition of embodiment 129 wherein the first GAS AI-1 polypeptide is selected from the group consisting of M6_Spy0157, M6_Spy0159, M6_Spy0160, CDC SS 410_fimbrial, ISS3650_fimbrial, DSM2071_fimbrial, and fragments thereof.

139. The immunogenic composition of embodiment 130 wherein the first GAS AI-2 polypeptide is selected from the group consisting of GAS15, GAS16, GAS18, and fragments thereof.

140. The immunogenic composition of embodiment 131 wherein the first GAS AI-3 polypeptide is selected from the group consisting of SpyM3_0098, SpyM3_0100, SpyM3_0102, SpyM3_0104, SPs0100, SPs0102, SPs0104, SPs0106, orf78, orf80, orf82, orf84, spyM18_0126, spyM18_0128, spyM18_0130, spyM18_0132, SpyoM01000156, SpyoM01000155, SpyoM01000154, SpyoM01000153, SpyoM01000152, SpyoM01000151, SpyoM01000150, SpyoM01000149, ISS3040_fimbrial, ISS3776_fimbrial, ISS4959_fimbrial, and fragments thereof.

141. The immunogenic composition of embodiment 132 wherein the first GAS AI-4 polypeptide is selected from the group consisting of 19224134, 19224135, 19224137, 19224139, 19224141, 20010296_fimbrial, 20020069_fimbrial, CDC SS 635_fimbrial, ISS4883_fimbrial, ISS4538_fimbrial, and fragments thereof.

142. The immunogenic composition of embodiment 134 wherein the second GAS AI-1 polypeptide is selected from the group consisting of M6_Spy0157, M6_Spy0159, M6_Spy0160, CDC SS 410_fimbrial, ISS3650_fimbrial, DSM2071_fimbrial, and fragments thereof.

143. The immunogenic composition of embodiment 135 wherein the second GAS AI-2 polypeptide is selected from the group consisting of GAS15, GAS16, GAS18, and fragments thereof.

144. The immunogenic composition of embodiment 136 wherein the second GAS AI-3 polypeptide is selected from the group consisting of SpyM3_0098, SpyM3_0100, SpyM3_0102, SpyM3_0104, SPs0100, SPs0102, SPs0104, SPs0106, orf78, orf80, orf82, orf84, spyM18_0126, spyM18_0128, spyM18_0130, spyM18_0132, SpyoM01000156, SpyoM01000155, SpyoM01000154, SpyoM01000153, SpyoM01000152, SpyoM01000151, SpyoM01000150, SpyoM01000149, ISS3040_fimbrial, ISS3776_fimbrial, ISS4959_fimbrial, and fragments thereof.

145. The immunogenic composition of embodiment 137 wherein the second GAS AI-4 polypeptide is selected from the group consisting of 19224134, 19224135, 19224137, 19224139, 19224141, 20010296_fimbrial, 20020069_fimbrial, CDC SS 635_fimbrial, ISS4883_fimbrial, ISS4538_fimbrial, and fragments thereof.

146. The immunogenic composition of any one of embodiments 117-132 or 138-141 wherein the second Gram positive bacteria AI polypeptide is a Group B Streptococcus (GBS) AI polypeptide.

147. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide comprises a sortase substrate motif.

148. The immunogenic composition of embodiment 147 wherein the sortase substrate motif is an LPXTG motif.

149. The immunogenic composition of embodiment 148 wherein the LPXTG motif is represented by the amino acid sequence XPXTG, wherein the X at amino acid position 1 is an L, an I, or an F and the X at amino acid position 3 is any amino acid residue.

150. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide affects the ability of GBS bacteria to adhere to epithelial cells.

151. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide affects the ability of GBS bacteria to invade epithelial cells.

152. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide affects the ability of GBS bacteria to translocate through an epithelial cell layer.

153. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is capable of associating with an epithelial cell surface.

154. The immunogenic composition of embodiment 146 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

155. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is a full-length GBS AI protein.

156. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is a fragment of a full-length GBS AI protein.

157. The immunogenic composition of embodiment 156 wherein the fragment comprises at least 7 contiguous amino acid residues of the GBS AI protein.

158. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is a GBS AI-1 polypeptide.

159. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is a GBS AI-2 polypeptide.

160. The immunogenic composition of embodiment 158 wherein the GBS AI-1 polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.

161. The immunogenic composition of embodiment 159 wherein the GBS AI-2 polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof.

162. The immunogenic composition of any one of embodiments 117-132 or 138-141 wherein the second Gram positive bacteria AI polypeptide is a *Streptococcus pneumoniae* AI polypeptide.

163. The immunogenic composition of embodiment 162 wherein the *S. pneumoniae* AI polypeptide comprises a sortase substrate motif.

164. The immunogenic composition of embodiment 163 wherein the sortase substrate motif is an LPXTG motif.

165. The immunogenic composition of embodiment 162 wherein the *S. pneumoniae* AI polypeptide affects the ability of *S. pneumoniae* to adhere to epithelial cells.

166. The immunogenic composition of embodiment 162 *S. pneumoniae* AI polypeptide affects the ability of *S. pneumoniae* to invade epithelial cells.

167. The immunogenic composition of embodiment 162 wherein the *S. pneumoniae* AI polypeptide affects the ability of *S. pneumoniae* to translocate through an epithelial cell layer.

168. The immunogenic composition of embodiment 162 wherein the *S. pneumoniae* AI polypeptide is capable of associating with an epithelial cell surface.

169. The immunogenic composition of embodiment 168 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

170. The immunogenic composition of embodiment 162 wherein the *S. pneumoniae* AI polypeptide is a full-length *S. pneumoniae* AI protein.

171. The immunogenic composition of embodiment 162 wherein the *S. pneumoniae* AI polypeptide is a fragment of a full-length *S. pneumoniae* AI protein.

172. The immunogenic composition of embodiment 162 wherein the fragment comprises at least 7 contiguous amino acid residues of the *S. pneumoniae* AI protein.

173. The immunogenic composition of embodiment 162 wherein the *S. pneumoniae* AI polypeptide is selected from the group consisting of SP0462, SP0463, SP0464, orf3_670, orf4_670, orf5_670, ORF3_14CSR, ORF4_14CSR, ORF5_14CSR, ORF3_19AH, ORF4_19AH, ORF5_19AH, ORF3_19FTW, ORF4_19FTW, ORF5_19FTW, ORF3_23FP, ORF4_23FP, ORF5_23FP, ORF3_23FTW, ORF4_23FTW, ORF5_23FTW, ORF3_6BF, ORF4_6BF, ORF5_6BF, ORF3_6BSP, ORF4_6BSP, ORF5_6BSP, ORF3_9VSP, ORF4_9VSP, ORF5_9VSP, and fragments thereof.

174. The immunogenic composition of any one of embodiments 105-117 wherein the first Gram positive bacteria AI polypeptide is in oligomeric form.

175. The immunogenic composition of embodiment 174 wherein the oligomeric form is a hyperoligomer.

176. The immunogenic composition of embodiment 174 wherein the second Gram positive bacteria AI polypeptide is in oligomeric form.

177. The immunogenic composition of embodiment 176 wherein the oligomeric form is a hyperoligomer.

178. The immunogenic composition of embodiment 176 wherein the first and the second Gram positive bacteria AI polypeptide are associated in a single oligomeric form.

179. The immunogenic composition of embodiment 178 wherein the first and the second Gram positive bacteria AI polypeptide are chemically associated.

180. The immunogenic composition of embodiment 178 wherein the first and the second Gram positive bacteria AI polypeptide are physically associated.

181. The immunogenic composition of any one of embodiments 105-117 further comprising a Gram positive bacteria polypeptide not associated with an AI.

182. The immunogenic composition of embodiment 181 wherein the Gram positive bacteria polypeptide not associated with an AI is selected from the group consisting of GBS 322 and GBS 276.

183. The immunogenic composition of embodiment 182 wherein the Gram positive bacteria polypeptide not associated with an AI is GBS 322.

184. A modified Gram positive bacterium adapted to produce increased levels of AI surface protein.

185. The modified Gram positive bacterium of embodiment 184 wherein the AI surface protein is in oligomeric form.

186. The modified Gram positive bacterium of embodiment 185 wherein the oligomeric form is a hyperoligomer.

187. The modified Gram positive bacterium of any one of embodiments 184-186 which is a Group B Streptococcus bacterium.

188. The modified Gram positive bacterium of any one of embodiments 184-186 which is a Group A Streptococcus bacterium.

189. The modified Gram positive bacterium of any one of embodiments 184-186 which is a non-pathogenic Gram positive bacterium.

190. The modified Gram positive bacterium of embodiment 189 wherein the non-pathogenic Gram positive bacterium is *Streptococus gordonii.*

191. The modified Gram positive bacterium of embodiment 189 wherein the non-pathogenic Gram positive bacterium is *Lactococcus lactis.*

192. The modified Gram positive bacterium of any one of embodiments 184-186 which has been inactivated and wherein the AI surface protein is exposed on the surface of the Gram positive bacterium.

193. The modified Gram positive bacterium of any one of embodiments 184-186 which has been attenuated and wherein the AI surface protein is exposed on the surface of the Gram positive bacterium.

194. The modified GBS bacterium of embodiment 187 which has been inactivated and wherein the AI surface protein is exposed on the surface of the GBS bacterium.

195. The modified GBS bacterium of embodiment 187 which has been attenuated and wherein the AI surface protein is exposed on the surface of the GBS bacterium.

196. The modified GAS bacterium of embodiment 188 which has been inactivated and wherein the AI surface protein is exposed on the surface of the GAS bacterium.

197. The modified GAS bacterium of embodiment 188 which has been attenuated and wherein the AI surface protein is exposed on the surface of the GAS bacterium.

198. The modified non-pathogenic bacterium of embodiment 189 which has been inactivated and wherein the AI surface protein is exposed on the surface of the non-pathogenic Gram positive bacterium.

199. The modified non-pathogenic bacterium of embodiment 189 which has been attenuated and wherein the AI surface protein is exposed on the surface of the non-pathogenic Gram positive bacterium.

200. A method for manufacturing an oligomeric adhesin island (AI) surface antigen comprising:

culturing a Gram positive bacterium that expresses an oligomeric AI surface antigen and

isolating the expressed oligomeric AI surface antigen.

201. The method of embodiment 200 wherein the step of isolating is performed by collecting said oligomeric AI surface antigen from Gram positive bacterium secretions in the Gram positive bacterium culture.

202. The method of embodiment 200 further comprising a step of purifying.

203. The method of embodiment 202 wherein the oligomeric AI surface antigen is purified from the Gram positive bacterium cell surface.

204. The method of embodiment 200 wherein the Gram positive bacterium is adapted for increased AI protein expression.

205. The method of any one of embodiments 200-204 wherein the Gram positive bacterium is a Group A Streptococcus bacterium.

206. The method of any one of embodiments 200-204 wherein the Gram positive bacterium is a Group B Streptococcus bacterium.

207. The method of any one of embodiments 200-204 wherein the oligomeric AI surface antigen is in hyperoligomeric form.

208. The method of embodiment 200 wherein the Gram positive bacterium expresses the oligomeric AI surface antigen recombinantly.

209. The method of embodiment 208 wherein the Gram positive bacterium further manipulated expresses at least 1 AI sortase.

210. The modified Gram positive bacterium of any one of embodiments 184-186 which is a *S. pneumoniae* bacterium.

211. The method of any one of embodiments 200-204 wherein the Gram positive bacterium is *S. pneumoniae.*

WE CLAIM:

1. An immunogenic composition comprising a purified Group B Streptococcus (GBS) adhesin island (AI) polypeptide in oligomeric form.

2. The immunogenic composition of claim 1 wherein the GBS AI polypeptide is selected from a GBS AI-1.

3. The immunogenic composition of claim 1 wherein the GBS AI polypeptide is selected from a GBS AI-2.

4. The immunogenic composition of claim 2 wherein the GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.

5. The immunogenic composition of claim 3 wherein the GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof.

6. The immunogenic composition of claim 4 wherein the GBS AI polypeptide is GBS 80.

7. The immunogenic composition of any of claims 1-6 wherein the oligomeric form is a hyperoligomer.

8 (22). An immunogenic composition comprising a purified Gram positive bacteria adhesin island (AI) polypeptide in an oligomeric form.

9 (23). The immunogenic composition of claim 8 wherein the Gram positive bacteria is of a genus selected from the group consisting of *Streptococcus*, *Enterococcus*, *Staphylococcus*, *Clostridium*, *Corynebacterium*, or *Listeria*.

10 (24). The immunogenic composition of claim 9 wherein the Gram positive bacteria is of the genus *Streptococcus*.

11 (35). The immunogenic composition of claim 10 wherein the genus *Streptococcus* bacteria is Group A Streptococcus (GAS) bacteria and the Gram positive bacteria AI polypeptide is a GAS AI polypeptide.

12 (36). The immunogenic composition of claim 11 wherein the GAS AI polypeptide is selected from a GAS AI-1.

13 (37). The immunogenic composition of claim 11 wherein the GAS AI polypeptide is selected from a GAS AI-2.

14 (38). The immunogenic composition of claim 11 wherein the GAS AI polypeptide is selected from a GAS AI-3.

15 (39). The immunogenic composition of claim 11 wherein the GAS AI polypeptide is selected from a GAS AI-4.

16 (66). The immunogenic composition of any one of claims 8-15 wherein the oligomeric form is a hyperoligomer.

17. An immunogenic composition comprising a first and a second Group B Streptococcus (GBS) adhesin island (AI) polypeptide.

18. The immunogenic composition of claim 17 wherein the first GBS AI polypeptide is encoded by a GBS AI-1.

19. The immunogenic composition of claim 18 wherein the second GBS AI polypeptide is encoded by a GBS AI-2.

20. The immunogenic composition of claim 18 wherein the first GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.

21. The immunogenic composition of claim 19 wherein the second GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof, and wherein the first and the second GBS AI polypeptide are not the same polypeptide.

22. The immunogenic composition of claim 19 wherein the first GBS AI polypeptide is GBS 80 and the second GBS AI polypeptide is GBS 67.

23. An immunogenic composition comprising a first and a second Gram positive bacteria adhesin island (AI) polypeptide.

24. The immunogenic composition of claim 23 wherein the Gram positive bacteria is *Streptococcus*, *Enterococcus*, *Staphylococcus*, *Clostridium*, *Corynebacterium*, or *Listeria*.

25. The immunogenic composition of claim 23 wherein the first Gram positive bacteria AI polypeptide is a first Group A Streptococcus (GAS) AI polypeptide.

26. The immunogenic composition of claim 25 wherein the first GAS AI polypeptide is a first GAS AI-1 polypeptide.

27. The immunogenic composition of claim 25 wherein the first GAS AI polypeptide is a first GAS AI-2 polypeptide.

28. The immunogenic composition of claim 25 wherein the first GAS AI polypeptide is a first GAS AI-3 polypeptide.

29. The immunogenic composition of claim 25 wherein the first GAS AI polypeptide is a first GAS AI-4 polypeptide.

30. The immunogenic composition of any one of claims 25-29 wherein the second Gram positive bacteria AI polypeptide is a second GAS AI polypeptide.

31. The immunogenic composition of claim 30 wherein the second GAS AI polypeptide is a second GAS AI-1 polypeptide.

32. The immunogenic composition of claim 30 wherein the second GAS AI polypeptide is a second GAS AI-2 polypeptide.

33. The immunogenic composition of claim 30 wherein the second GAS AI polypeptide is a second GAS AI-3 polypeptide.

34. The immunogenic composition of claim 30 wherein the second GAS AI polypeptide is a second GAS AI-4 polypeptide.

35. A modified Gram positive bacterium adapted to produce increased levels of AI surface protein.

36. The modified Gram positive bacterium of claim 35 wherein the AI surface protein is in oligomeric form.

37. The modified Gram positive bacterium of claim 36 wherein the oligomeric form is a hyperoligomer.

38. The modified Gram positive bacterium of any one of claims 35-37 which is a non-pathogenic Gram positive bacterium.

39. The modified Gram positive bacterium of claim 38 wherein the non-pathogenic Gram positive bacterium is *Lactococcus lactis.*

40. A method for manufacturing an oligomeric adhesin island (AI) surface antigen comprising:

culturing a Gram positive bacterium that expresses an oligomeric AI surface antigen and

isolating the expressed oligomeric AI surface antigen.

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FIGURE 1: Adhesion Island 1

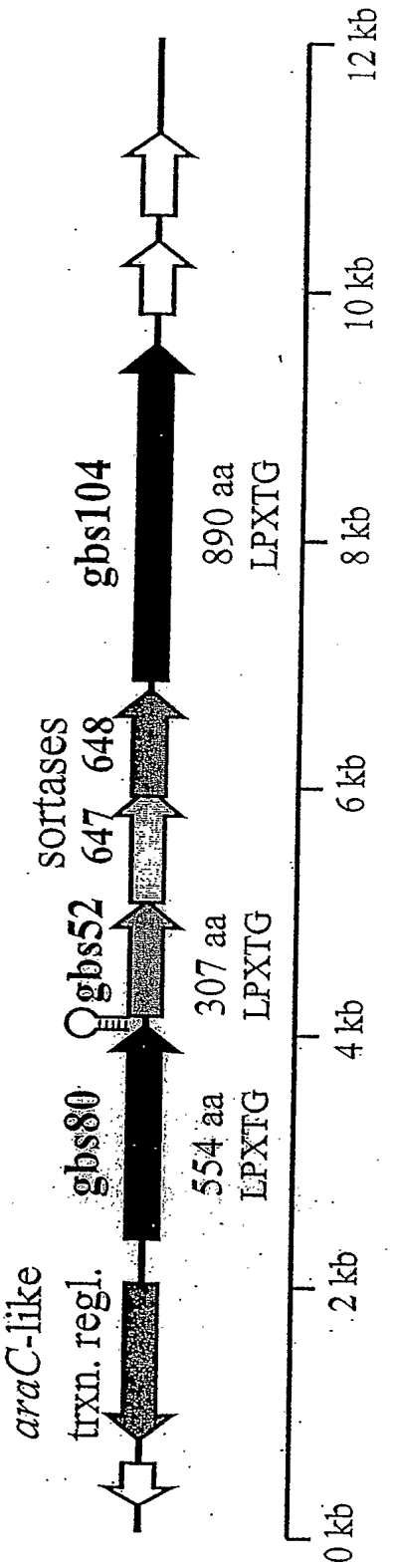

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Figure 2: Conservation of AI-1 in GBS serotypes and strain isolates

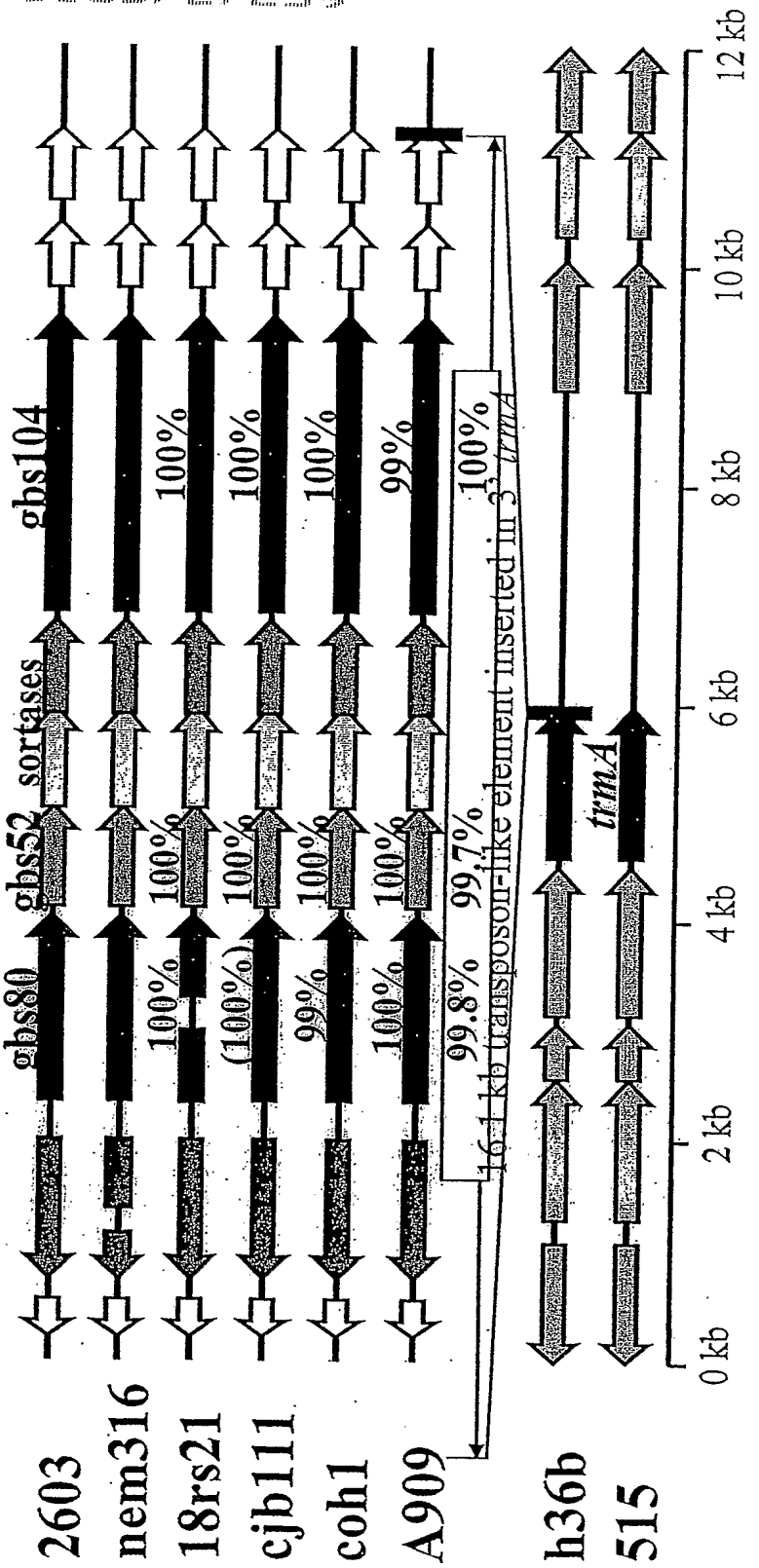


FIGURE 3: Correlation of AI-1 and AI-2 within GBS serotype V, strain isolate 2603 genome

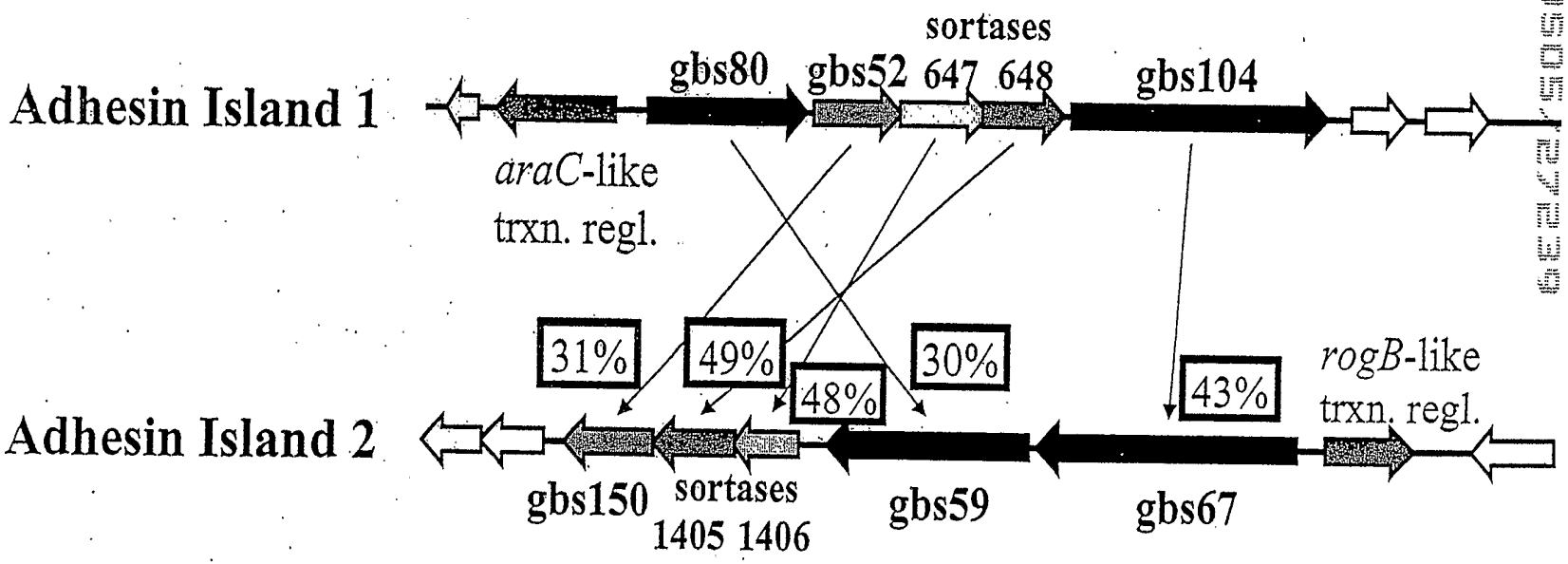


Figure 4: Identification and Variance of AI-2 in Several GBS Serotypes and Strain Isolates

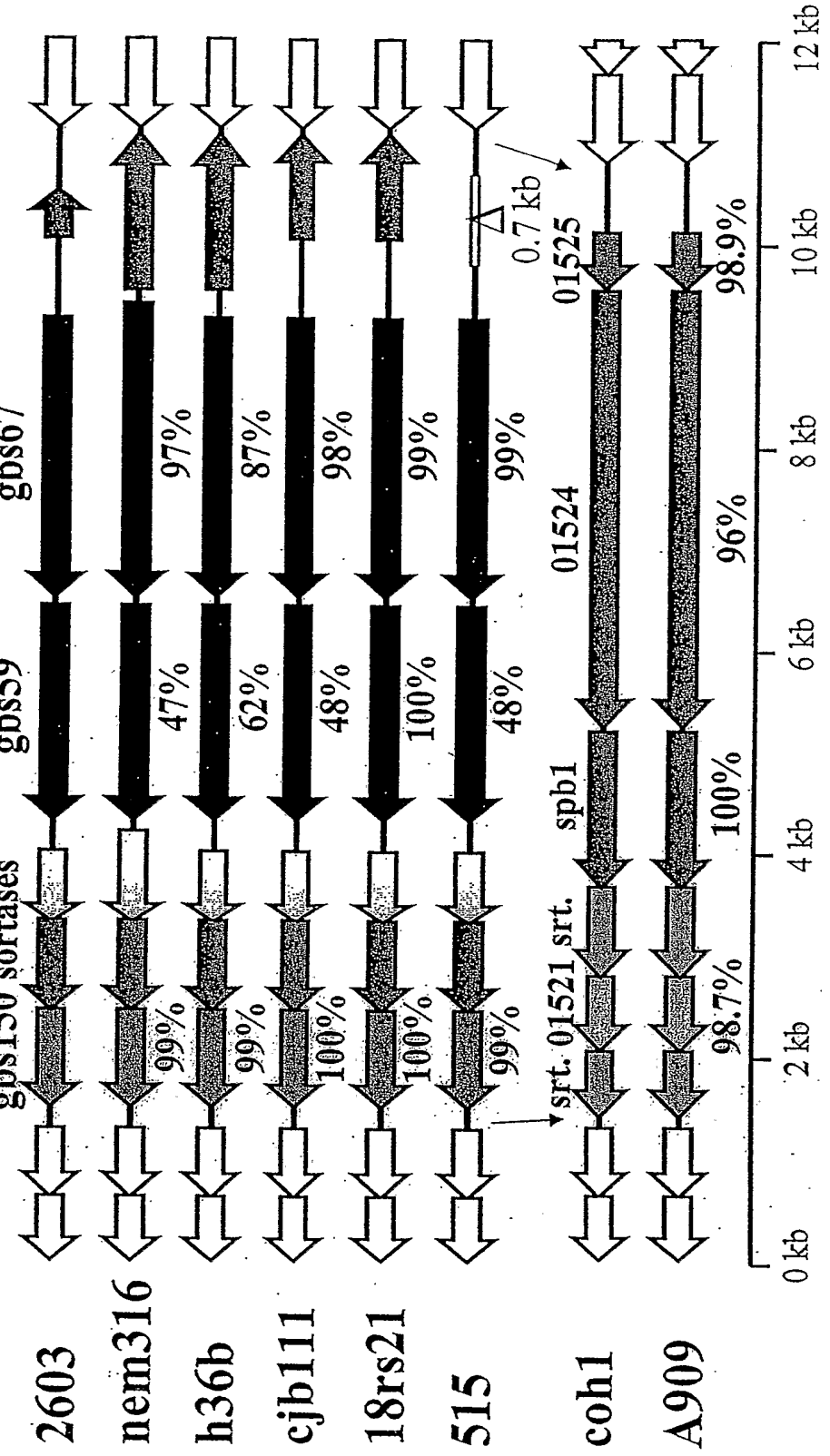


Figure 5: Purified gbs80 protein binds fibronectin and fibrinogen in an ELISA

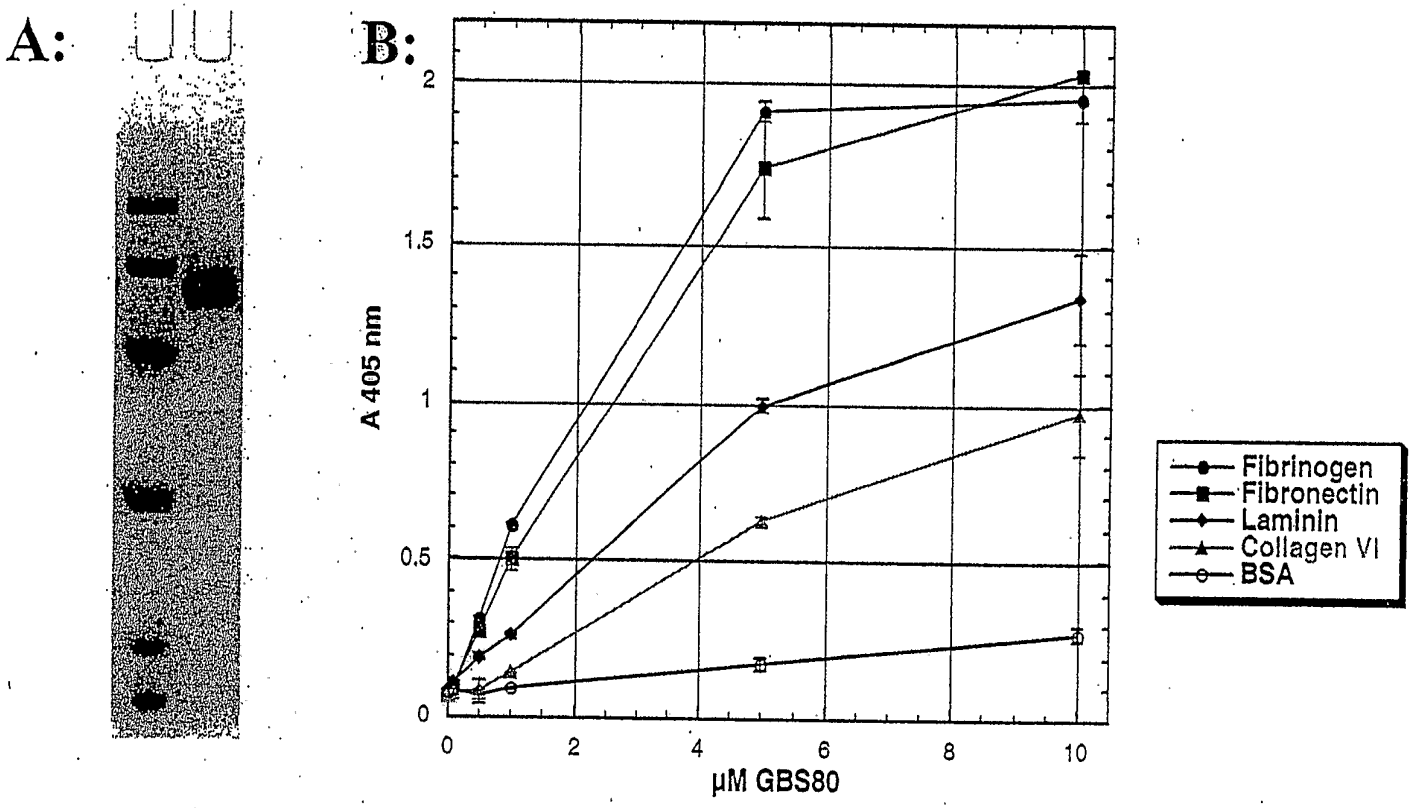


Figure 6: Adhesion Island I is an operon by RT-PCR

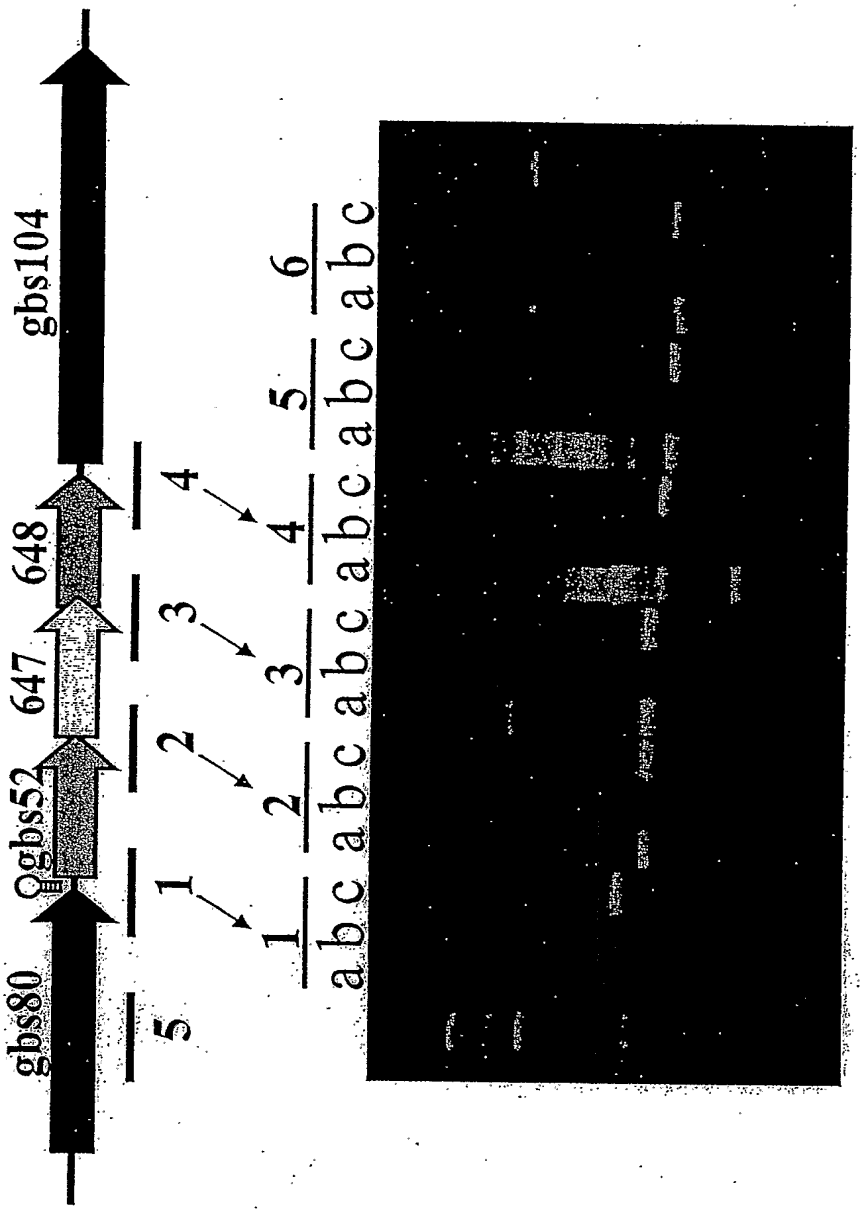


Figure 7: In frame deletions of AI-1 genes

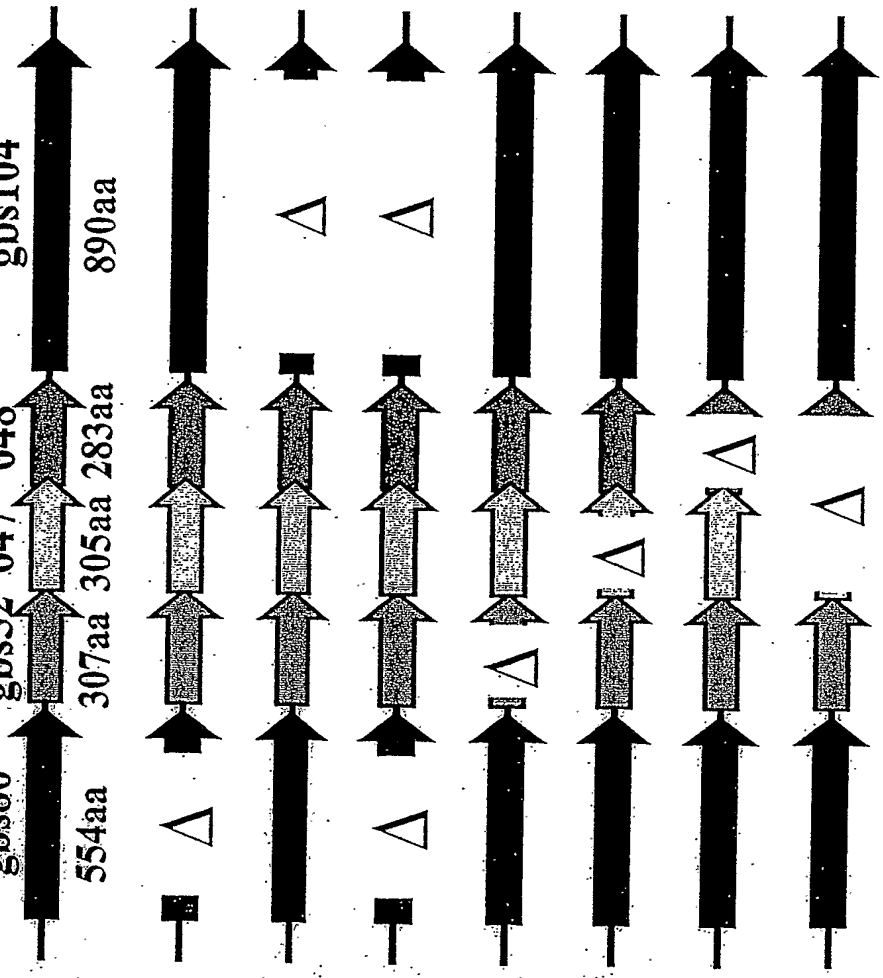


Figure 8: gbs80 is required for surface localization of gbs104

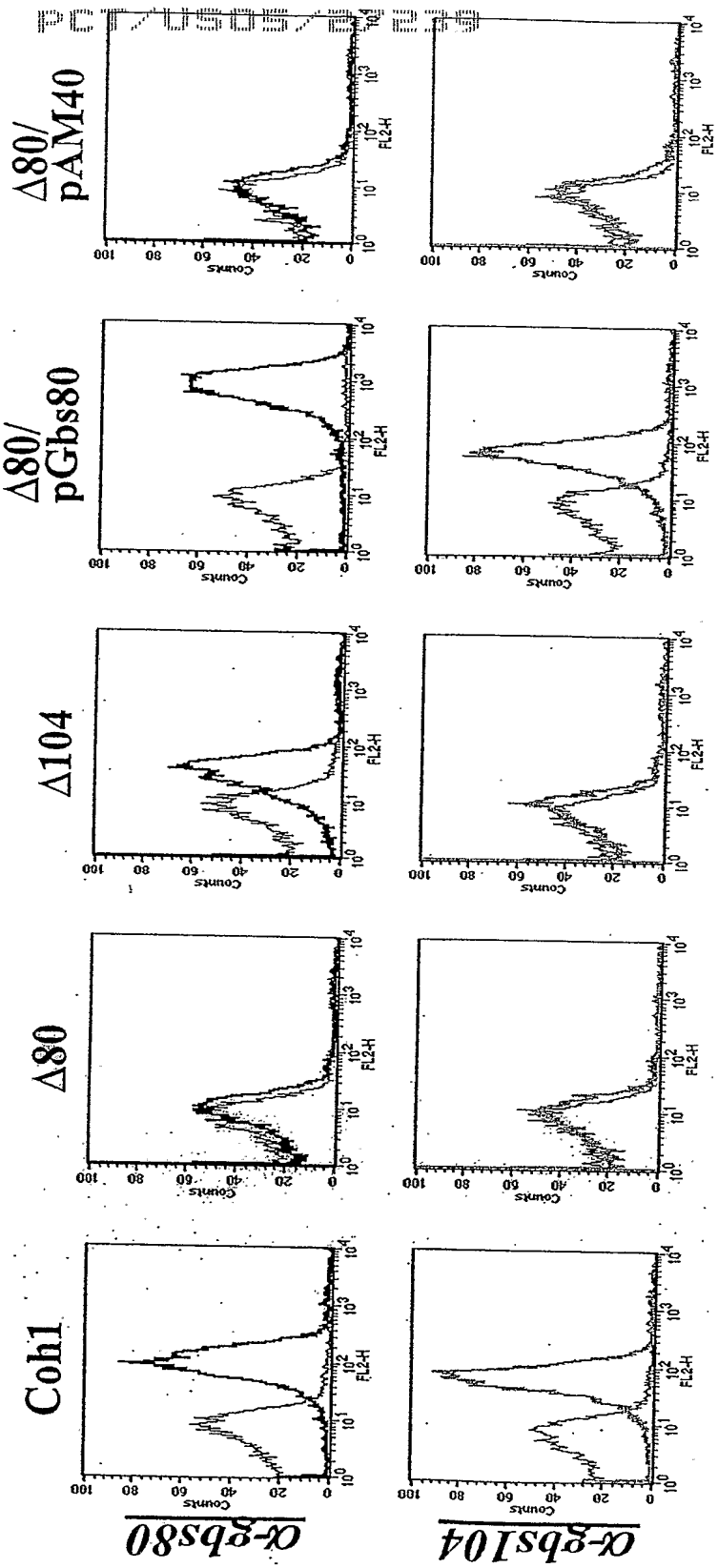


Figure 9: sortases 647 & 648 play a semi-redundant role in surface exposure of gbs80 and gbs104

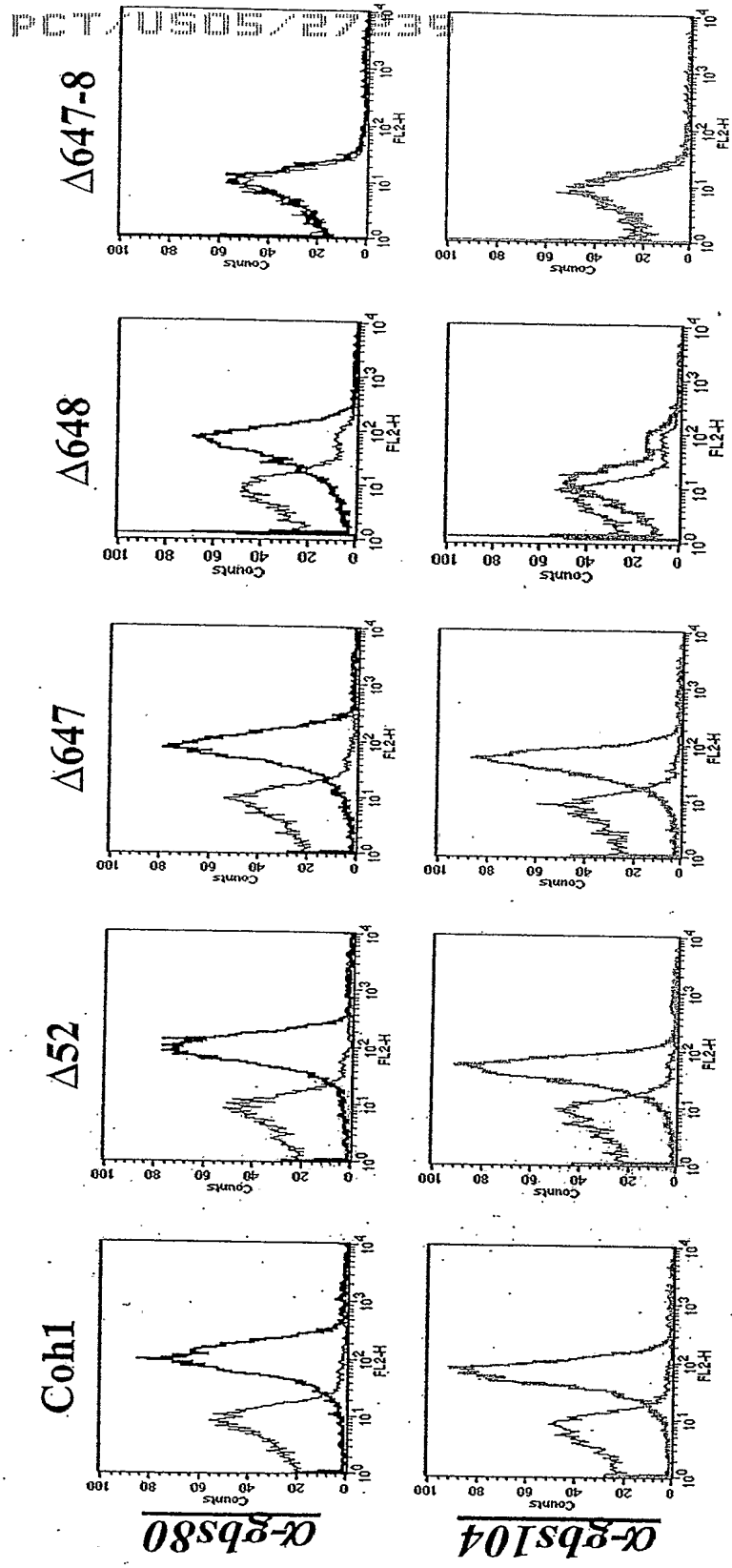
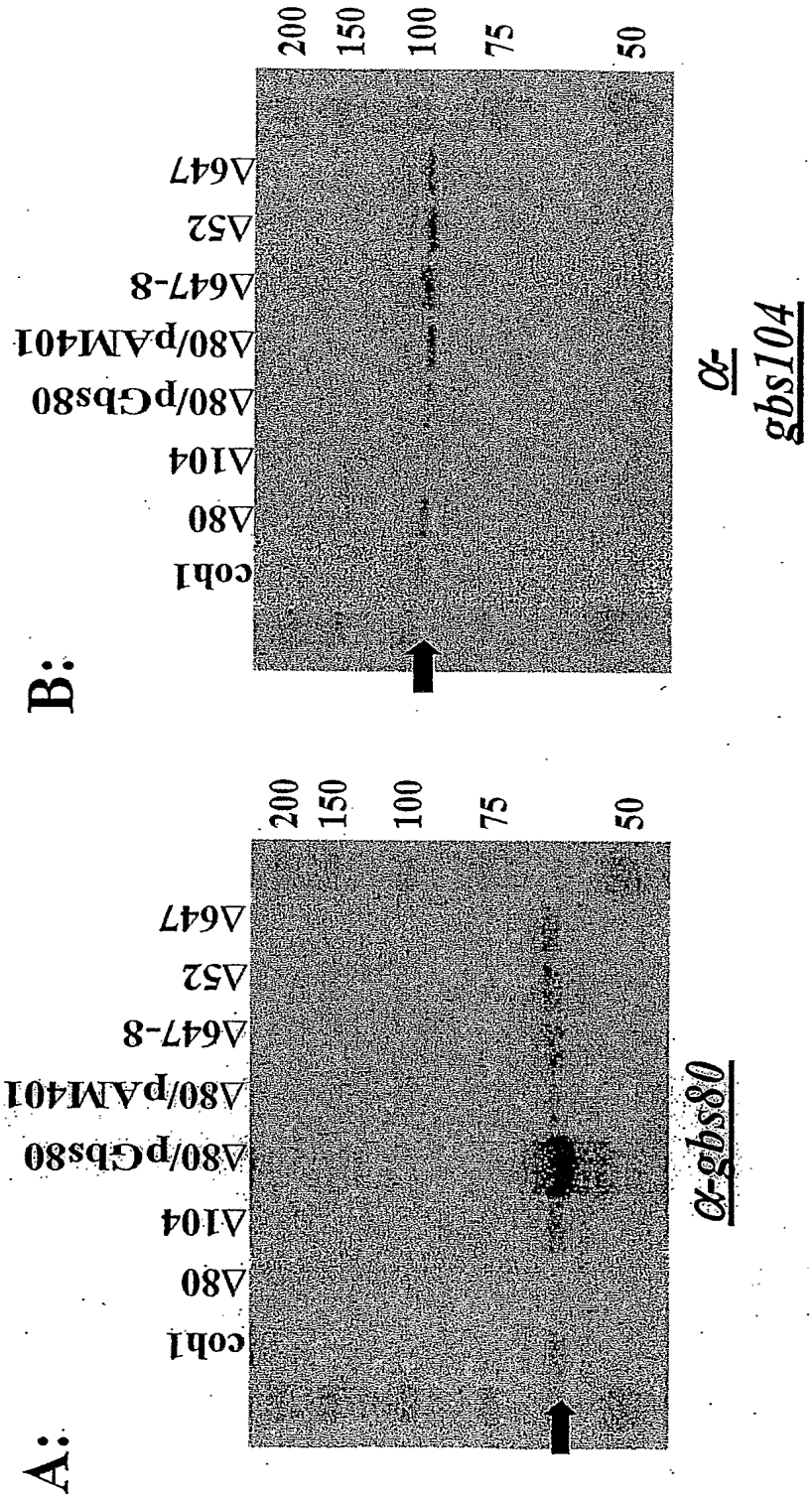


Figure 10: Western blot of mutant strains



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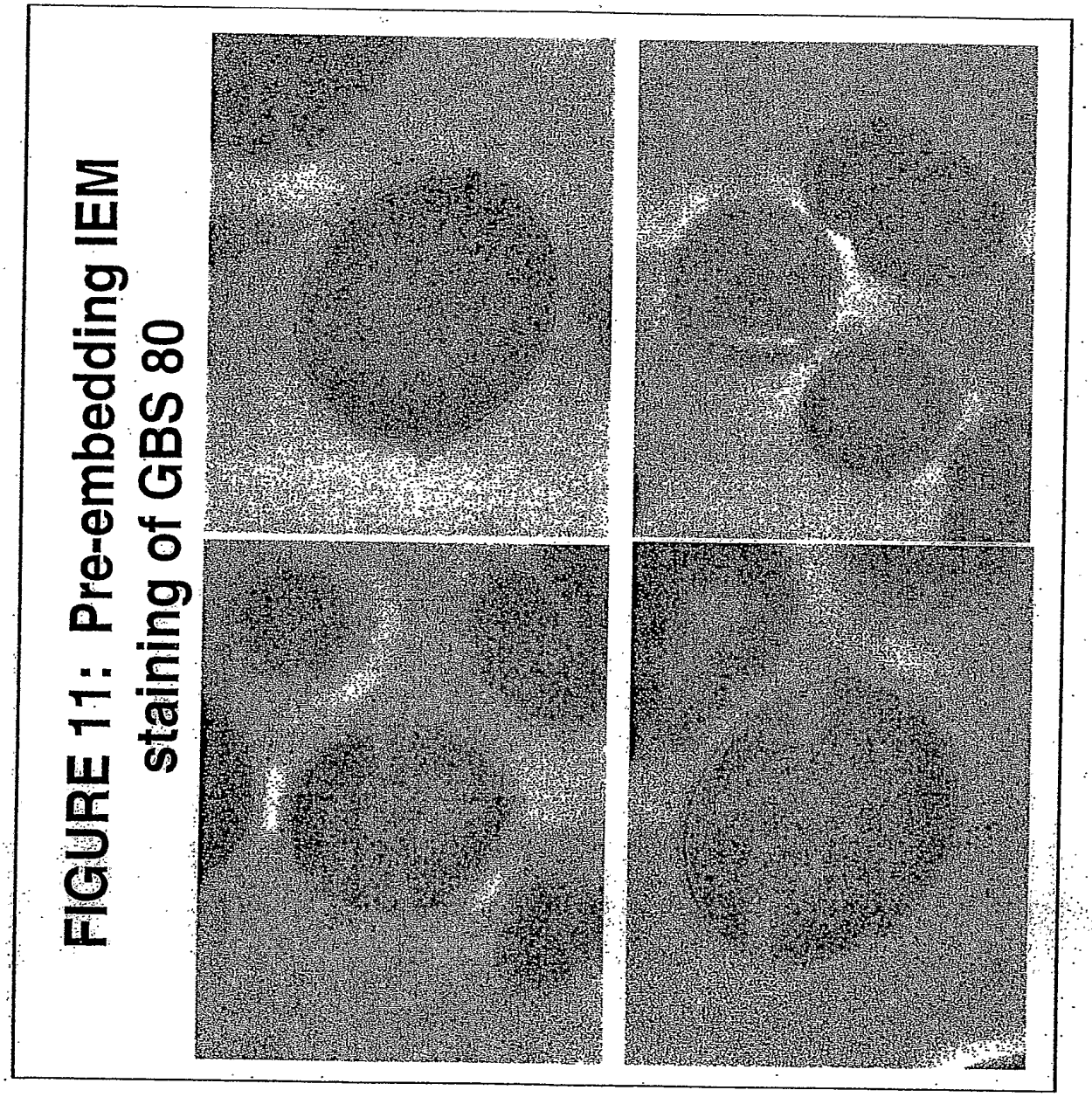

FIGURE 11: Pre-embedding IEM staining of GBS 80

FIGURE 12: Predicted Secondary Structure for GBS 067

PHD SECONDARY STRUCTURE PREDICTION for GBS 067

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         10        20        30        40        50        60        70
          |         |         |         |         |         |         |
MRKYQKFSKILTLSLFCLSQIPLNTNVLGESTVPENGAKGKLVVKKTDDQNKPLSKATFVLKTTAHPESK
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KQYPPTGIYEDTKESYKLEHVKGSVPNGKSEAKAVNPYSSEGEHIREIPEGTLSKRISEVGDLAHNKYKI
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ELTVSGKTIVKPVDKQKPLDVVFVLDNSNSMNNDGPNFQRHNKAKKAAEALGTAVKDILGANSDNRVALV
EEEccCcEEEecCCCCCCCeEEEEEcCCCCCCCCCCCCCCChhHHHHHHHHHHHHHHHHHhcCcCCeEEEE
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TPEQQKEYYLSKVGETFTMKAFMEADDILSQVNRNSQKIIVHVTDGVPTRSYAINNFKLGASYESQFEQM
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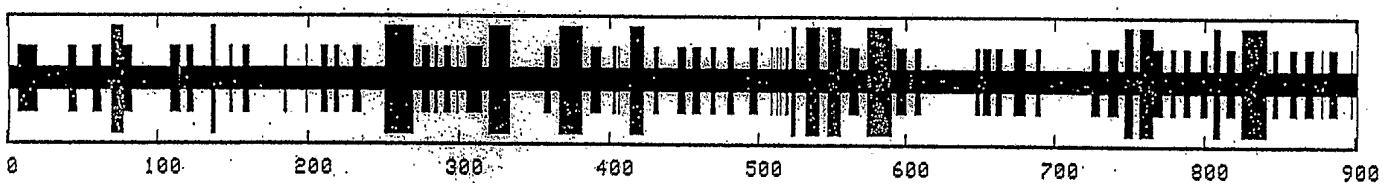
Sequence length : 901

PHD :

Alpha helix	(Hh)	:	148 is	16.43%	3_{10} helix	(Gg)	:	0 is 0.00%
Pi helix	(Ii)	:	0 is	0.00%	Beta bridge	(Bb)	:	0 is 0.00%
Extended strand	(Ee)	:	243 is	26.97%	Beta turn	(Tt)	:	0 is 0.00%
Bend region	(Ss)	:	0 is	0.00%	Random coil	(Cc)	:	510 is 56.60%
Ambigous states	(?)	:	0 is	0.00%	Other states		:	0 is 0.00%



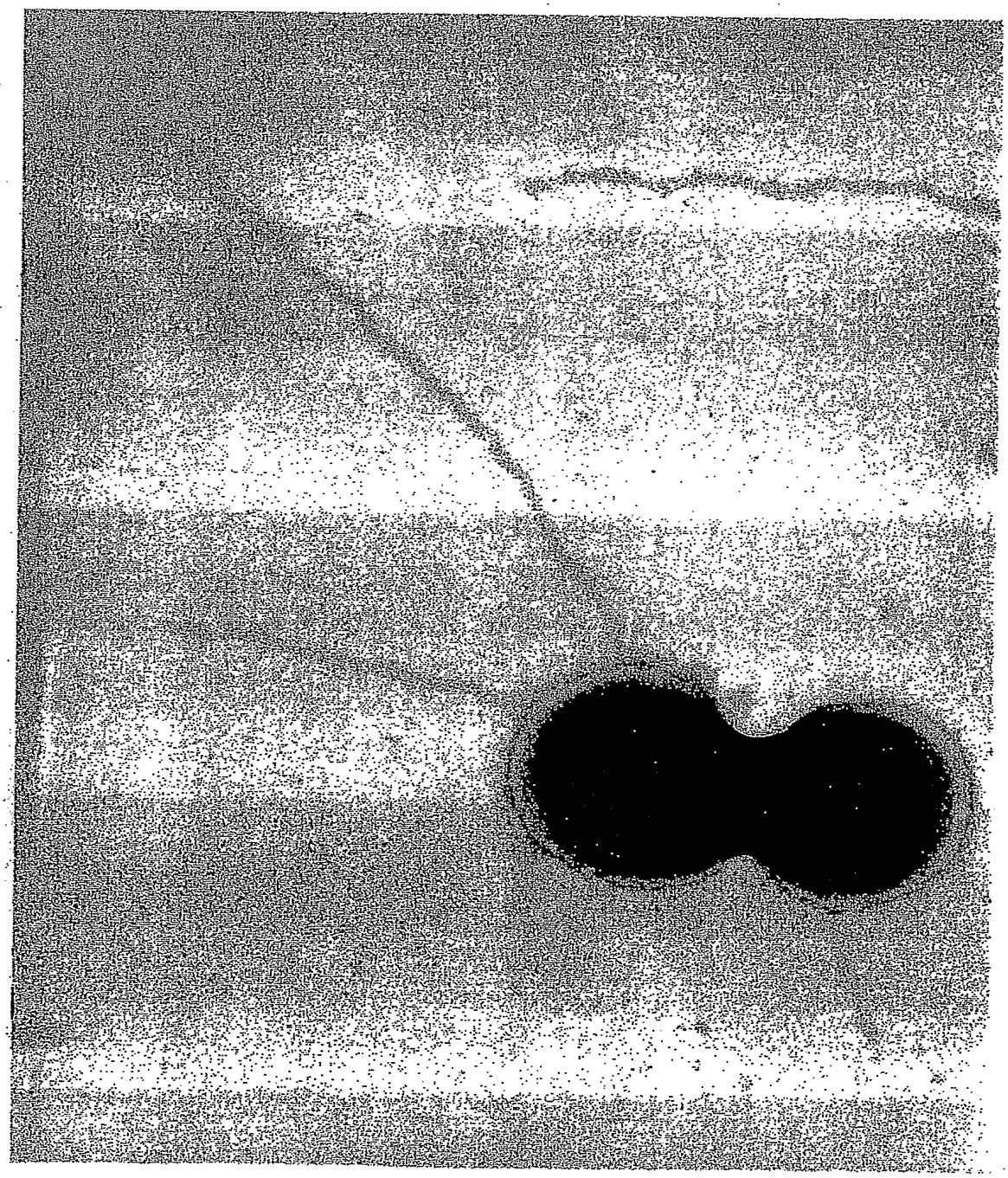


Figure 13

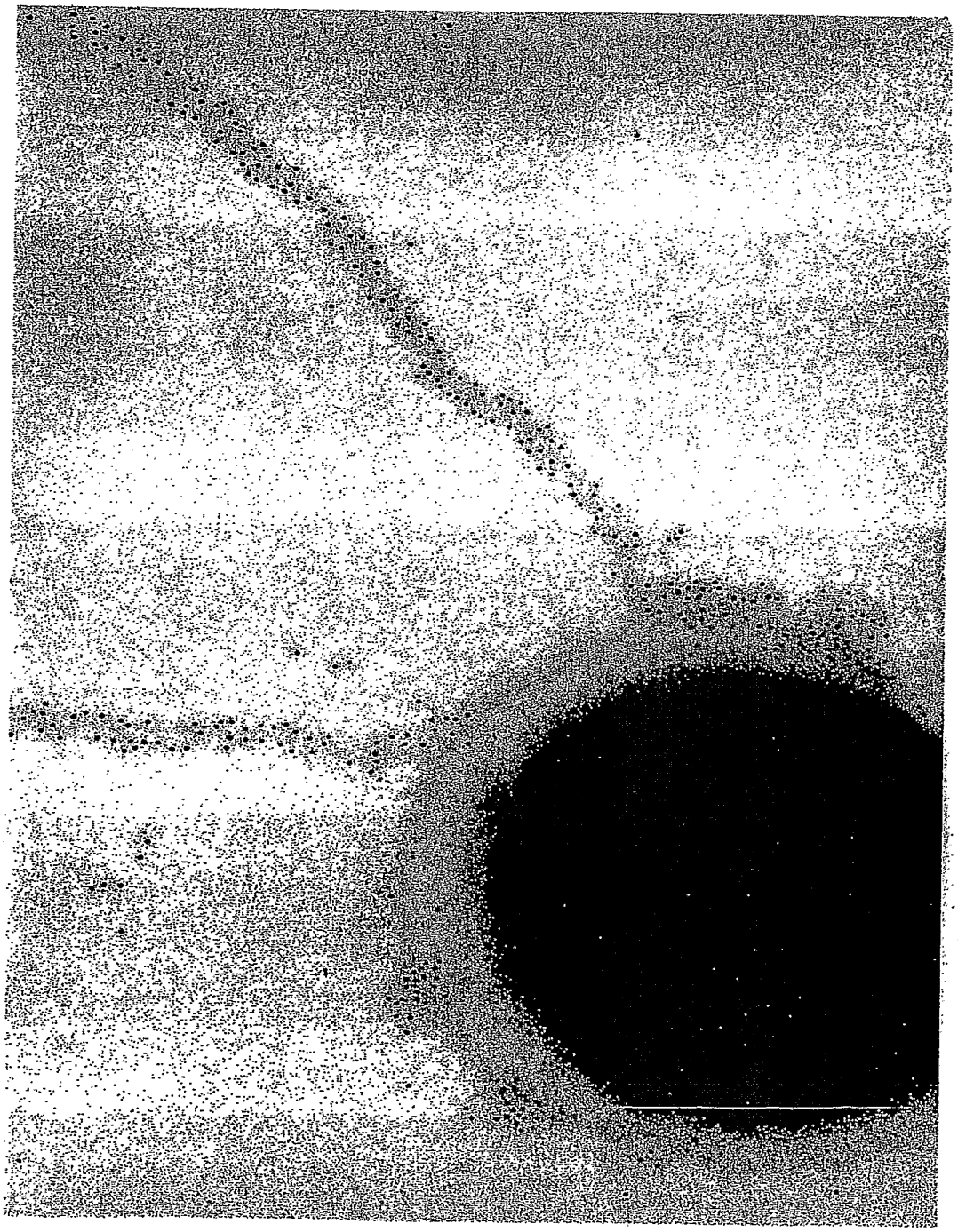
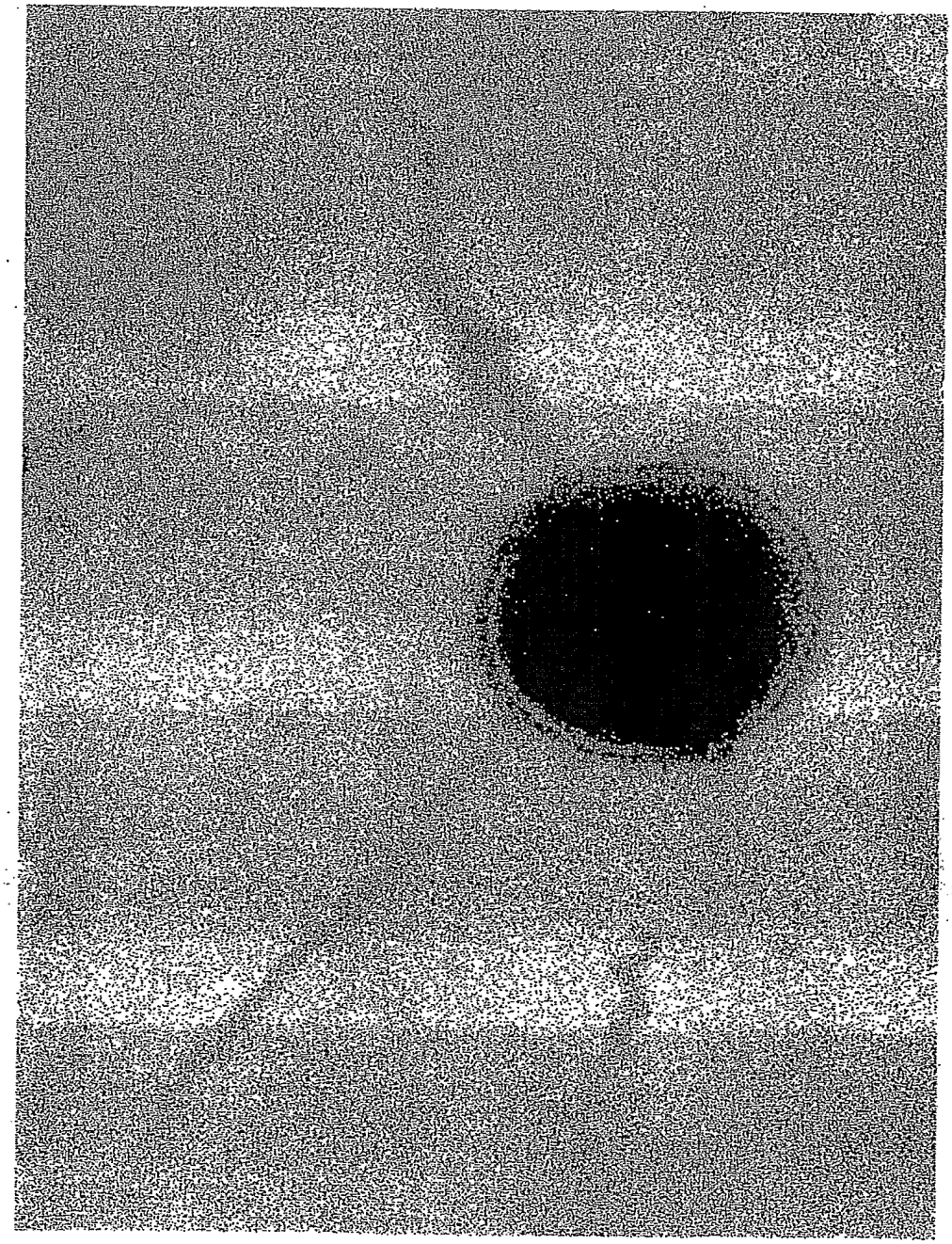


Figure 14



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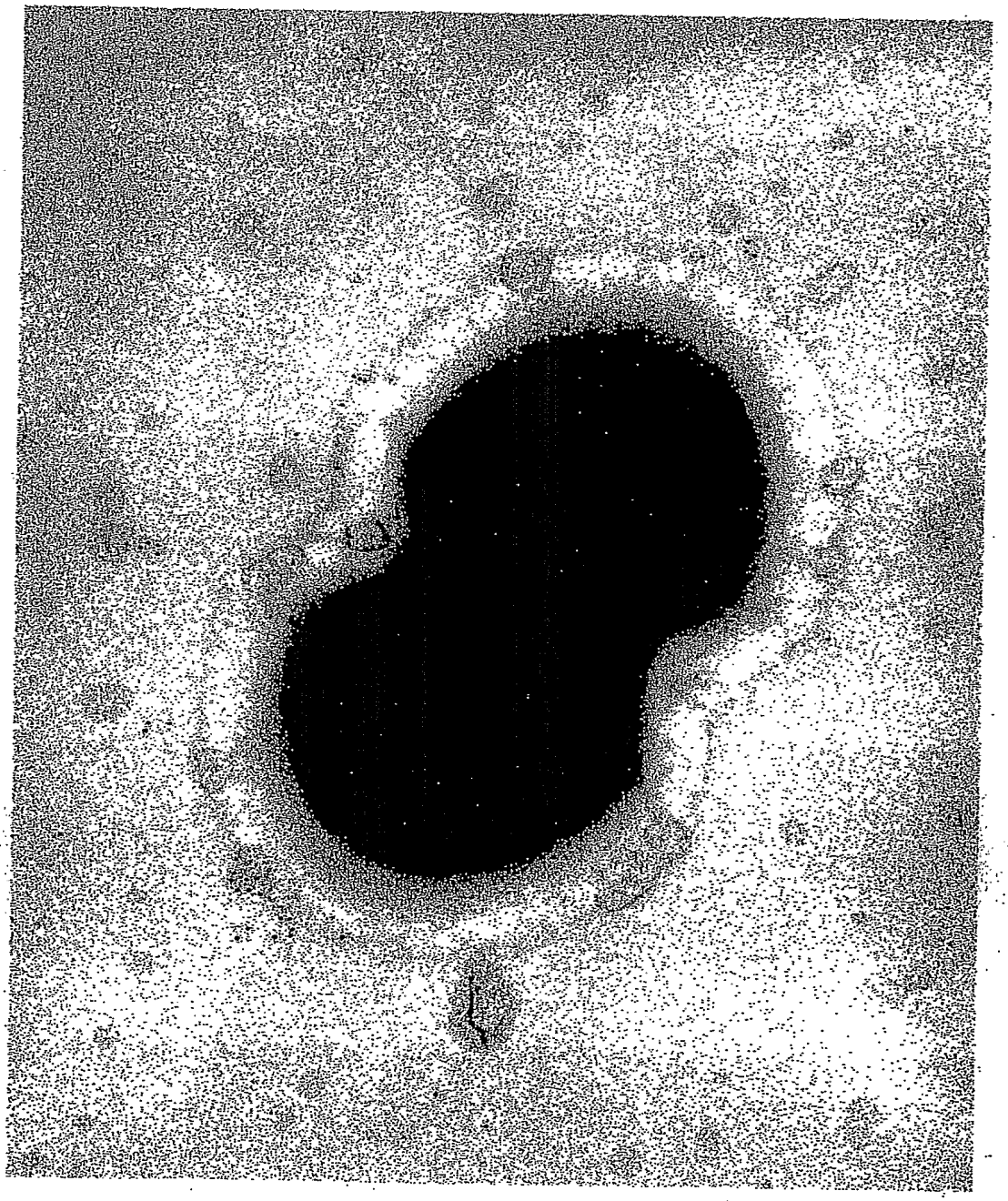

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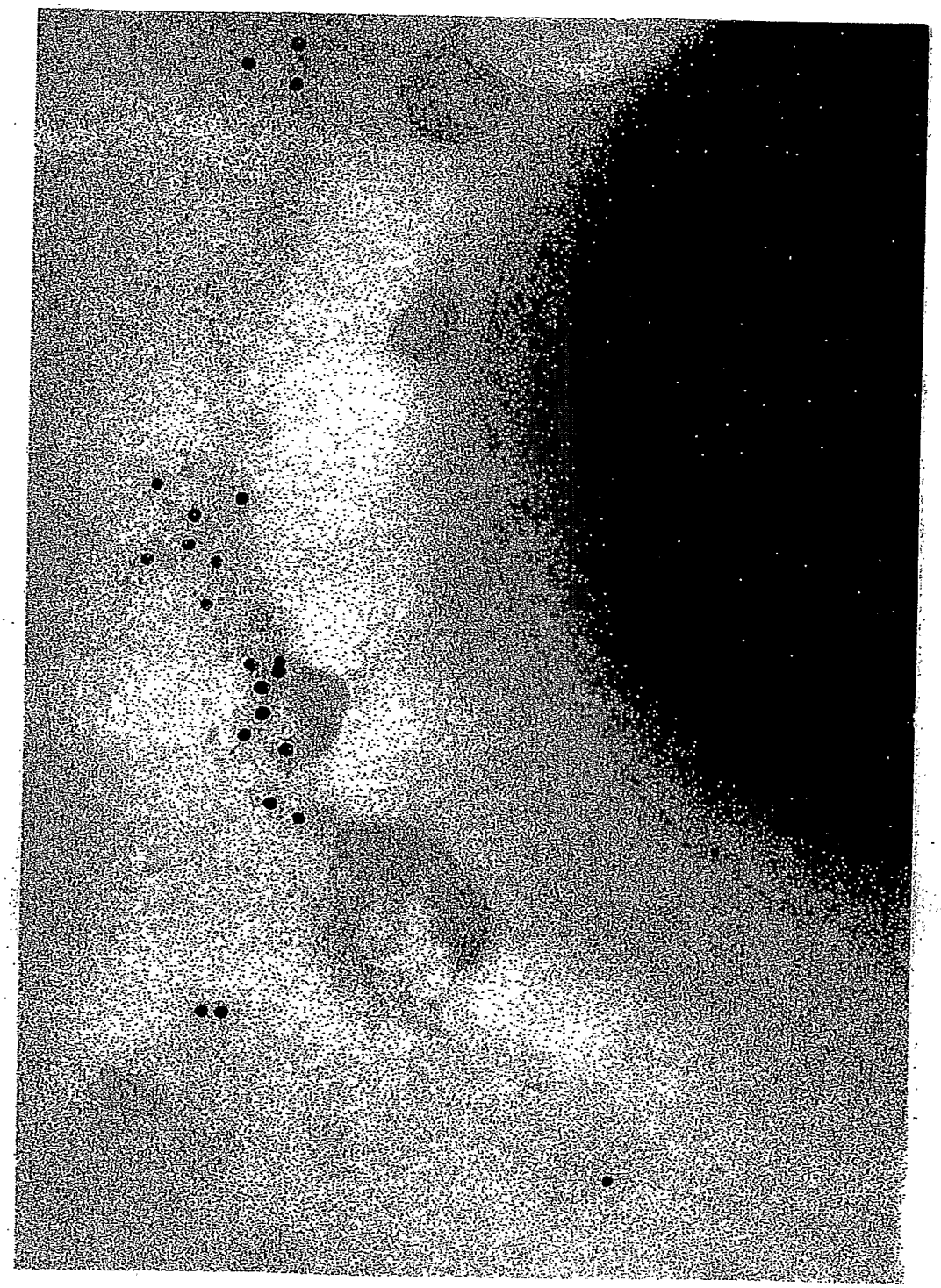

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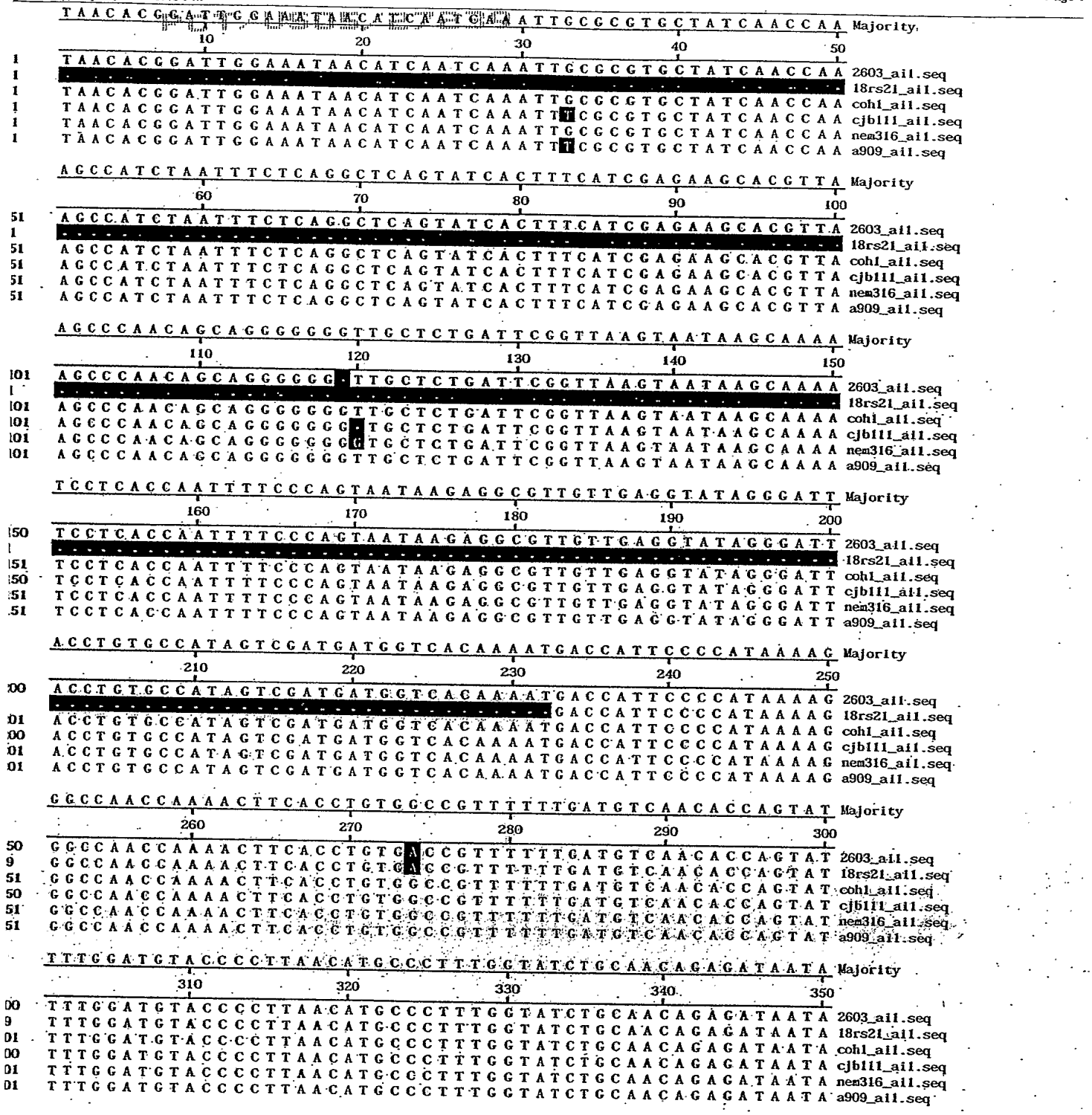
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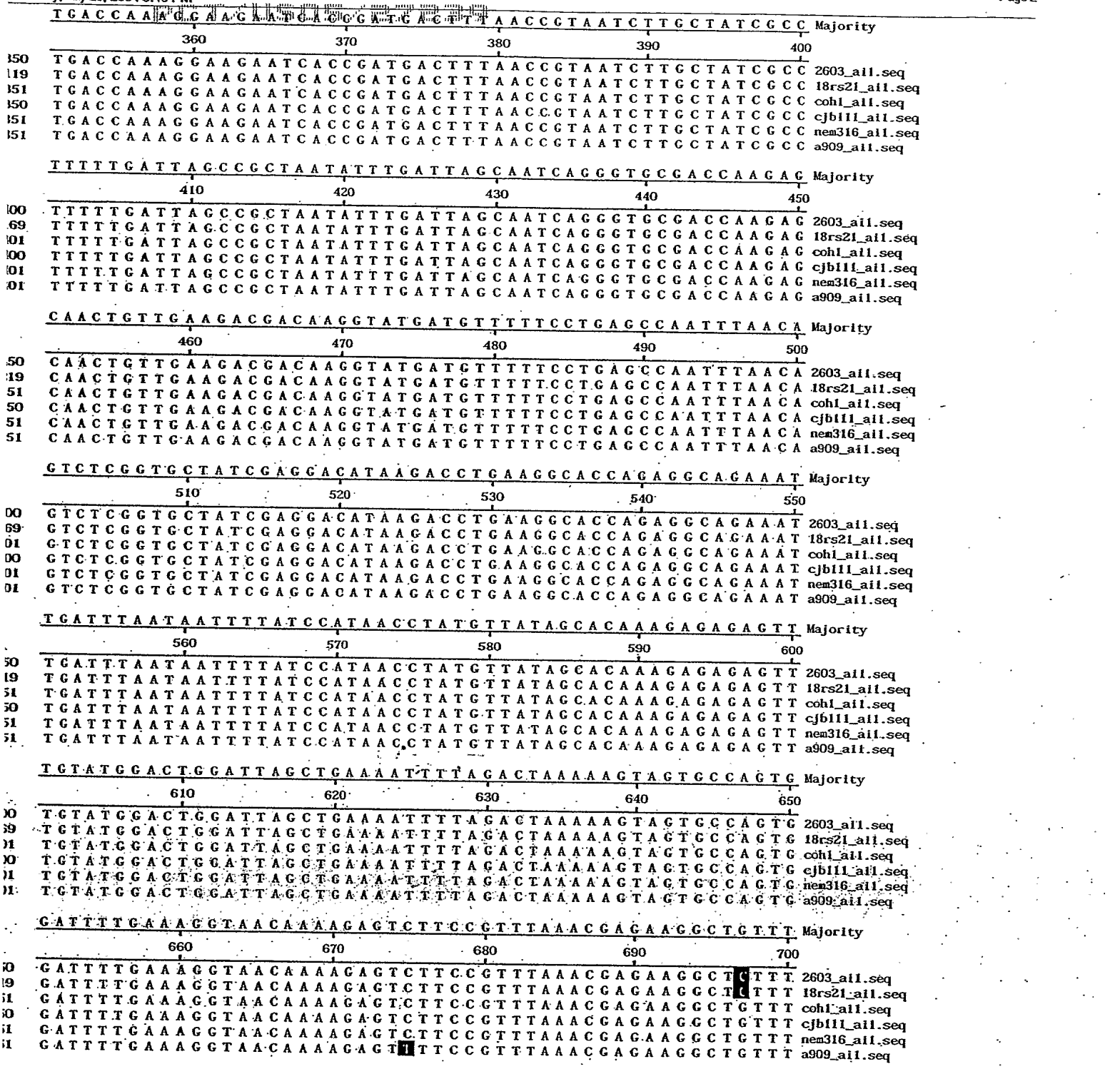
Figure 18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a909_all.seq

FIGURE 18 A

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00  TTAGTCGTTTCAGATGAAGGCAAAAGGACGATGAAATAATTCCGTACCTT cjb111_ai1.seq
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50  CATGGATTGCTATGTTACTGGCATGAGGTCTCACGATATTTAGTAAGATA 2603_ai1.seq
19  CATGGATTGCTATGTTACTGGCATGAGGTCTCACGATATTTAGTAAGATA 18rs21_ai1.seq
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```

FIGURE 18 B

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819  AGGTGGTTGTCCACATAATGGAGAATACTATTGTACATTTGCTGCTTGTC 18rs21_ai1.seq
1051 AGGTGGTTGTCCACATAATGGAGAATACTATTGTACATTTGCTGCTTGTC coh1_ai1.seq
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              1110      1120      1130      1140      1150
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869  AGAGATGCTCTTATTGGTTAAGGATTCTGAAAAATCAATAAGAGCTGCAC 18rs21_ai1.seq
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     AGCGAATTCTTGAAACATCAATAAGATCAGGAGCCTCTTCGTTTAAAGCC Majority
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919  AGCGAATTCTTGAAACATCAATAAGATCAGGAGCCTCTTCGTTTAAAGCC 18rs21_ai1.seq
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FIGURE 18 C

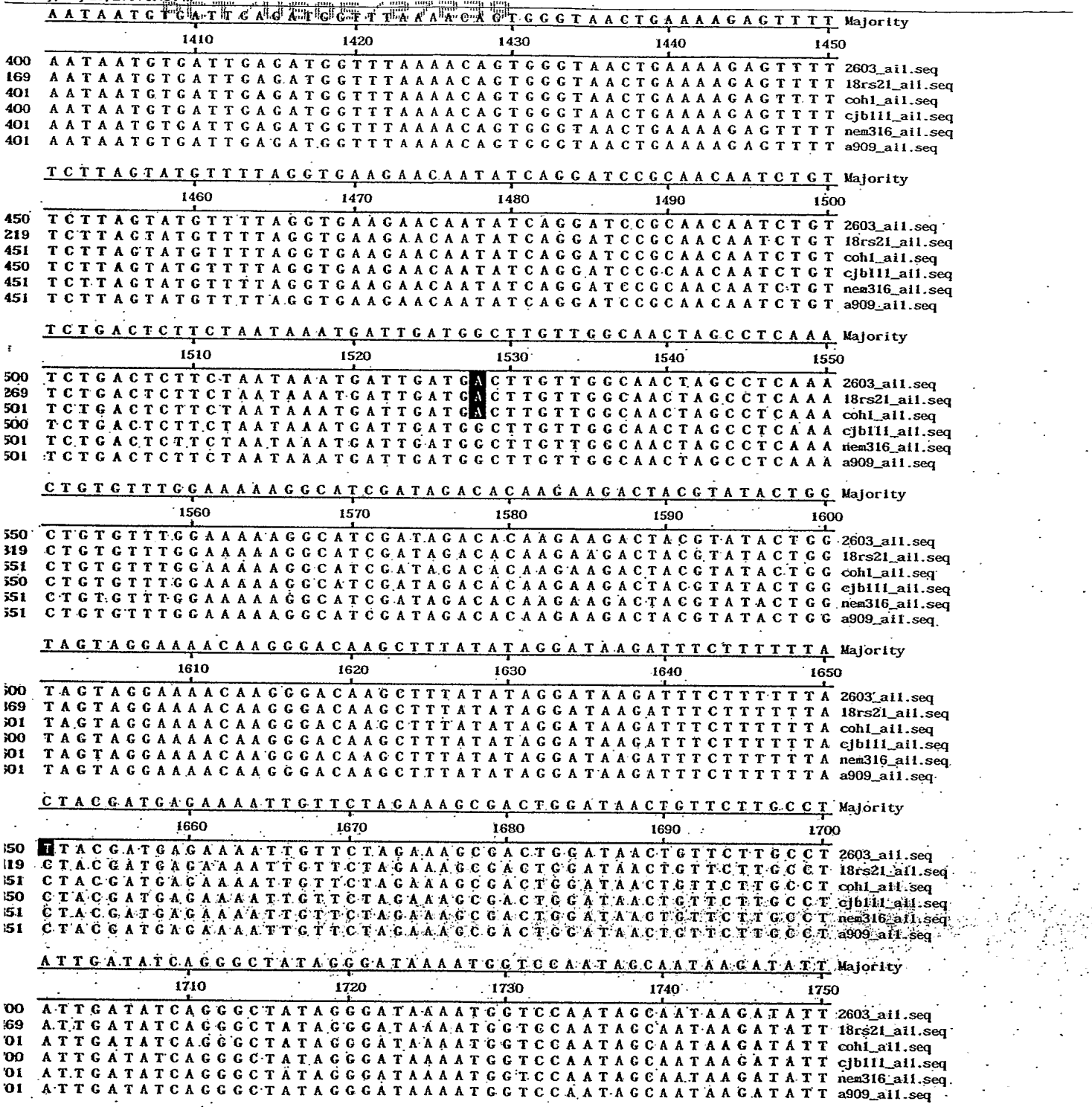
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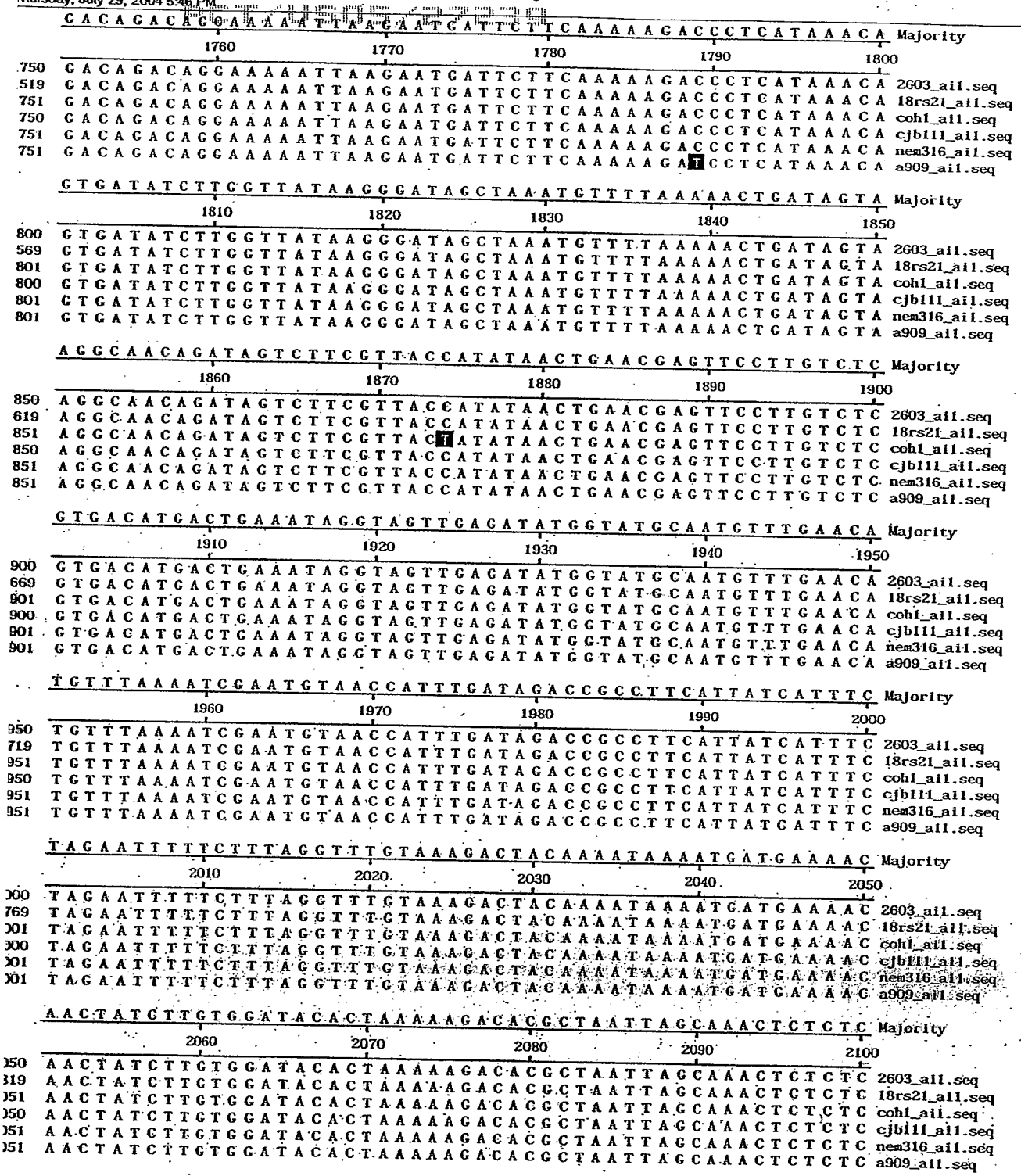
FIGURE 18 D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1810 1820 1830 1840 1850
800 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA
569 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA 2603_all.seq
801 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA 18rs21_all.seq
800 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA cohl_all.seq
801 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA cjb111_all.seq
801 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA nem316_all.seq
801 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA a909_all.seq
AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC Majority
1860 1870 1880 1890 1900
850 AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC
619 AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC 2603_all.seq
851 AGGCAACAGATAGTCTTCGTTACTATATAACTGAACGAGTTCCTTGTCTC 18rs21_all.seq
850 AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC cohl_all.seq
851 AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC cjb111_all.seq
851 AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC nem316_all.seq
851 AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC a909_all.seq
GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA Majority
1910 1920 1930 1940 1950
900 GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA
669 GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA 2603_all.seq
901 GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA 18rs21_all.seq
900 GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA cohl_all.seq
901 GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA cjb111_all.seq
901 GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA nem316_all.seq
901 GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA a909_all.seq
TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC Majority
1960 1970 1980 1990 2000
950 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC
719 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC 2603_all.seq
951 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC 18rs21_all.seq
950 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC cohl_all.seq
951 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC cjb111_all.seq
951 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC nem316_all.seq
951 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC a909_all.seq
TAGAATTTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAAC Majority
2010 2020 2030 2040 2050
000 TAGAATTTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAAC
769 TAGAATTTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAAC 2603_all.seq
001 TAGAATTTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAAC 18rs21_all.seq
000 TAGAATTTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAAC cohl_all.seq
001 TAGAATTTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAAC cjb111_all.seq
001 TAGAATTTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAAC nem316_all.seq
AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC Majority
2060 2070 2080 2090 2100
050 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC
819 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC 2603_all.seq
051 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC 18rs21_all.seq
050 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC cohl_all.seq
051 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC cjb111_all.seq
051 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC nem316_all.seq
051 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC a909_all.seq

FIGURE 18 E

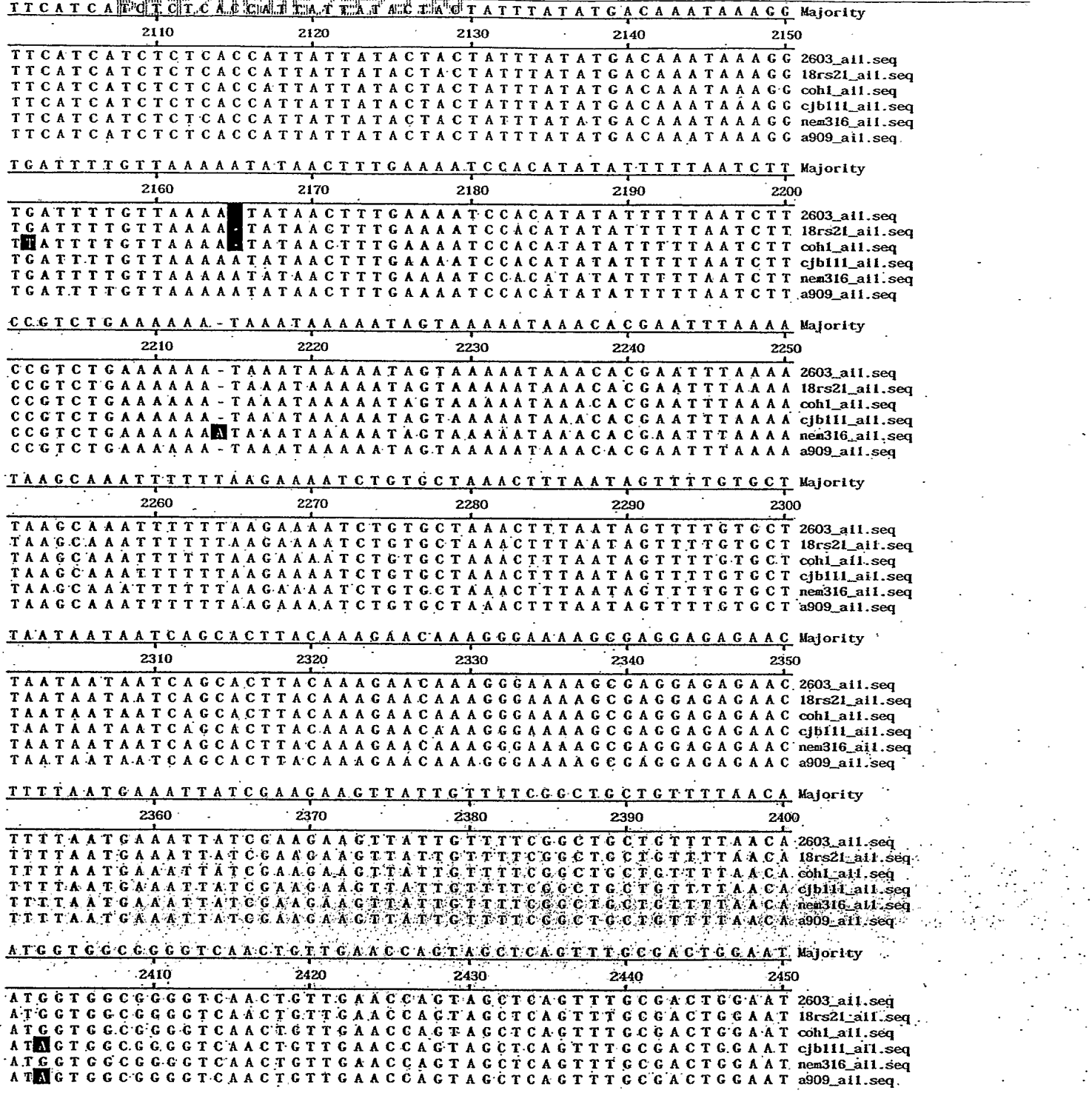
Majority
2603_all.seq
18rs21_all.seq
cohl_all.seq
cjb111_all.seq
nem316_all.seq
a909_all.seq

FIGURE 18 F

```
     GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA Majority
              2460      2470      2480      2490      2500
2448 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA 2603_ail.seq
2217 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA 18rs21_ail.seq
2449 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA cohl_ail.seq
2449 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA cjb111_ail.seq
2451 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA nem316_ail.seq
2450 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA a909_ail.seq

     CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT Majority
              2510      2520      2530      2540      2550
2498 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT 2603_ail.seq
2267 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT 18rs21_ail.seq
2499 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT cohl_ail.seq
2499 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT cjb111_ail.seq
2501 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT nem316_ail.seq
2500 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT a909_ail.seq

     TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC Majority
              2560      2570      2580      2590      2600
2548 TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC 2603_ail.seq
2317 TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC 18rs21_ail.seq
2549 TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC cohl_ail.seq
2549 TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC cjb111_ail.seq
2551 TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC nem316_ail.seq
2550 TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC a909_ail.seq

     TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT Majority
              2610      2620      2630      2640      2650
2598 TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT 2603_ail.seq
2367 TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT 18rs21_ail.seq
2599 TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT cohl_ail.seq
2599 TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT cjb111_ail.seq
2601 TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT nem316_ail.seq
2600 TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT a909_ail.seq

     ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA Majority
              2660      2670      2680      2690      2700
2648 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA 2603_ail.seq
2417 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA 18rs21_ail.seq
2649 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA cohl_ail.seq
2649 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA cjb111_ail.seq
2651 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA nem316_ail.seq
2650 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA a909_ail.seq

     GTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAG Majority
              2710      2720      2730      2740      2750
2698 GTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAG 2603_ail.seq
2467 GTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAG 18rs21_ail.seq
2699 GTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAG cohl_ail.seq
2699 GTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAG cjb111_ail.seq
2701 GTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAG nem316_ail.seq
2700 GTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAG a909_ail.seq

     TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT Majority
              2760      2770      2780      2790      2800
2748 TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT 2603_ail.seq
2517 TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT 18rs21_ail.seq
2749 TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT cohl_ail.seq
2749 TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT cjb111_ail.seq
2751 TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT nem316_ail.seq
2750 TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT a909_ail.seq
```

FIGURE 18 G

```
CAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCT Majority

                2810        2820        2830        2840        2850
2798 CAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCT 2603_all.seq
2567 CAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCT 18rs21_all.seq
2799 CAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCT coh1_all.seq
2799 CAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCT cjb111_all.seq
2801 CAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCT nem316_all.seq
2800 CAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCT a909_all.seq

TCAAACATTACCAAAGCTTATGCTGTACCGTTTGTGTTGGAATTACCAGT Majority

                2860        2870        2880        2890        2900
2848 TCAAACATTACCAAAGCTTATGCTGTACCGTTTGTGTTGGAATTACCAGT 2603_all.seq
2617 TCAAACATTACCAAAGCTTATGCTGTACCGTTTGTGTTGGAATTACCAGT 18rs21_all.seq
2849 TCAAACATTACCAAAGCTTATGCTGTACCGTTTGTGTTGGAATTACCAGT coh1_all.seq
2849 TCAAACATTACCAAAGCTTATGCTGTACCGTTTGTGTTGGAATTACCAGT cjb111_all.seq
2851 TCAAACATTACCAAAGCTTATGCTGTACCGTTTGTGTTGGAATTACCAGT nem316_all.seq
2850 TCAAACATTACCAAAGCTTATGCTGTACCGTTTGTGTTGGAATTACCAGT a909_all.seq

TGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTA Majority

                2910        2920        2930        2940        2950
2898 TGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTA 2603_all.seq
2667 TGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTA 18rs21_all.seq
2899 TGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTA coh1_all.seq
2899 TGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTA cjb111_all.seq
2901 TGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTA nem316_all.seq
2900 TGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTA a909_all.seq

AAAACGTTGTAACTGATGAACCAAAAAACAGATAAAGATGTTAAAAAATTA Majority

                2960        2970        2980        2990        3000
2948 AAAACGTTGTAACTGATGAACCAAAAAACAGATAAAGATGTTAAAAAATTA 2603_all.seq
2717 AAAACGTTGTAACTGATGAACCAAAAAACAGATAAAGATGTTAAATAATTA 18rs21_all.seq
2949 AAAACGTTGTAACTGATGAACCAAAAAACAGATAAAGATGTTAAAAAATTA coh1_all.seq
2949 AAAACGTTGTAACTGATGAACCAAAAAACAGATAAAGATGTTAAAAAATTA cjb111_all.seq
2951 AAAACGTTGTAACTGATGAACCAAAAAACAGATAAAGATGTTAAAAAATTA nem316_all.seq
2950 AAAACGTTGTAACTGATGAACCAAAAAACAGATAAAGATGTTAAAAAATTA a909_all.seq

GGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAATGGTTCTT Majority

                3010        3020        3030        3040        3050
2998 GGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAATGGTTCTT 2603_all.seq
2767 GGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAATGGTTCTT 18rs21_all.seq
2999 GGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAATGGTTCTT coh1_all.seq
2999 GGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAATGGTTCTT cjb111_all.seq
3001 GGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAATGGTTCTT nem316_all.seq
3000 GGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAATGGTTCTT a909_all.seq

GAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTA Majority

                3060        3070        3080        3090        3100
3048 GAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTA 2603_all.seq
3017 GAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTA 18rs21_all.seq
3049 GAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTA coh1_all.seq
3049 GAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTA cjb111_all.seq
3051 GAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTA nem316_all.seq
3050 GAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTA a909_all.seq

CTGATAAATTTGCAGATGGCTTGACTTATAAATCTGTTGCAAAAATCAAG Majority

                3110        3120        3130        3140        3150
3098 CTGATAAATTTGCAGATGGCTTGACTTATAAATCTGTTGCAAAAATCAAG 2603_all.seq
3067 CTGATAAATTTGCAGATGGCTTGACTTATAAATCTGTTGCAAAAATCAAG 18rs21_all.seq
3099 CTGATAAATTTGCAGATGGCTTGACTTATAAATCTGTTGCAAAAATCAAG coh1_all.seq
3099 CTGATAAATTTGCAGATGGCTTGACTTATAAATCTGTTGCAAAAATCAAG cjb111_all.seq
3101 CTGATAAATTTGCAGATGGCTTGACTTATAAATCTGTTGCAAAAATCAAG nem316_all.seq
3100 CTGATAAATTTGCAGATGGCTTGACTTATAAATCTGTTGCAAAAATCAAG a909_all.seq
```

FIGURE 18 H

	ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC	Majority
	3160 3170 3180 3190 3200	
148	ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC	2603_ai1.seq
917	ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC	18rs21_ai1.seq
149	ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC	coh1_ai1.seq
149	ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC	cjb111_ai1.seq
151	ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC	nem316_ai1.seq
150	ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC	a909_ai1.seq

	AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT	Majority
	3210 3220 3230 3240 3250	
198	AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT	2603_ai1.seq
967	AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT	18rs21_ai1.seq
199	AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT	coh1_ai1.seq
199	AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT	cjb111_ai1.seq
201	AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT	nem316_ai1.seq
200	AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT	a909_ai1.seq

	TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA	Majority
	3260 3270 3280 3290 3300	
248	TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA	2603_ai1.seq
017	TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA	18rs21_ai1.seq
249	TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA	coh1_ai1.seq
249	TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA	cjb111_ai1.seq
251	TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA	nem316_ai1.seq
250	TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA	a909_ai1.seq

	GATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGA	Majority
	3310 3320 3330 3340 3350	
298	GATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGA	2603_ai1.seq
067	GATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGA	18rs21_ai1.seq
299	GATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGA	coh1_ai1.seq
299	GATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGA	cjb111_ai1.seq
301	GATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGA	nem316_ai1.seq
300	GATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGA	a909_ai1.seq

	AATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTTTTAGGAAAAGCAA	Majority
	3360 3370 3380 3390 3400	
48	AATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTTTTAGGAAAAGCAA	2603_ai1.seq
17	AATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTTTTAGGAAAAGCAA	18rs21_ai1.seq
49	AATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTTTTAGGAAAAGCAA	coh1_ai1.seq
49	AATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTTTTAGGAAAAGCAA	cjb111_ai1.seq
51	AATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTTTTAGGAAAAGCAA	nem316_ai1.seq
50	AATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTTTTAGGAAAAGCAA	a909_ai1.seq

	TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC	Majority
	3410 3420 3430 3440 3450	
98	TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC	2603_ai1.seq
67	TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC	18rs21_ai1.seq
99	TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC	coh1_ai1.seq
99	TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC	cjb111_ai1.seq
01	TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC	nem316_ai1.seq
00	TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC	a909_ai1.seq

	AATCCAAAACCATCTAATCCTCCAAGAAAACCAGAAGTTCATACTGGTGG	Majority
	3460 3470 3480 3490 3500	
48	AATCCAAAACCATCTAATCCTCCAAGAAAACCAGAAGTTCATACTGGTGG	2603_ai1.seq
17	AATCCAAAACCATCTAATCCTCCAAGAAAACCAGAAGTTCATACTGGTGG	18rs21_ai1.seq
49	AATCCAAAACCATCTAATCCTCCAAGAAAACCAGAAGTTCATACTGGTGG	coh1_ai1.seq
49	AATCCAAAACCATCTAATCCTCCAAGAAAACCAGAAGTTCATACTGGTGG	cjb111_ai1.seq
51	AATCCAAAACCATCTAATCCTCCAAGAAAACCAGAAGTTCATACTGGTGG	nem316_ai1.seq
50	AATCCAAAACCATCTAATCCTCCAAGAAAACCAGAAGTTCATACTGGTGG	a909_ai1.seq

FIGURE 18 I

```
GAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTG Majority

                3510        3520        3530        3540        3550
1498 GAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTG 2603_all.seq
1267 GAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTG 18rs21_all.seq
1499 GAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTG cohl_all.seq
1499 GAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTG cjb111_all.seq
1501 GAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTG nem316_all.seq
1500 GAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTG a909_all.seq

CTGAGTTTGATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGAT Majority

                3560        3570        3580        3590        3600
1548 CTGAGTTTGATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGAT 2603_all.seq
1317 CTGAGTTTGATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGAT 18rs21_all.seq
1549 CTGAGTTTGATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGAT cohl_all.seq
1549 CTGAGTTTGATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGAT cjb111_all.seq
1551 CTGAGTTTGATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGAT nem316_all.seq
1550 CTGAGTTTGATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGAT a909_all.seq

GCTCTTATTAAAGCCGAATACTAATAAAAACTATATTGCTGGAGAAGCTGT Majority

                3610        3620        3630        3640        3650
1598 GCTCTTATTAAAGCCGAATACTAATAAAAACTATATTGCTGGAGAAGCTGT 2603_all.seq
1367 GCTCTTATTAAAGCCGAATACTAATAAAAACTATATTGCTGGAGAAGCTGT 18rs21_all.seq
1599 GCTCTTATTAAAGCCGAATACTAATAAAAACTATATTGCTGGAGAAGCTGT cohl_all.seq
1599 GCTCTTATTAAAGCCGAATACTAATAAAAACTATATTGCTGGAGAAGCTGT cjb111_all.seq
1601 GCTCTTATTAAAGCCGAATACTAATAAAAACTATATTGCTGGAGAAGCTGT nem316_all.seq
1600 GCTCTTATTAAAGCCGAATACTAATAAAAACTATATTGCTGGAGAAGCTGT a909_all.seq

TACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGA Majority

                3660        3670        3680        3690        3700
1648 TACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGA 2603_all.seq
1417 TACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGA 18rs21_all.seq
1649 TACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGA cohl_all.seq
1649 TACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGA cjb111_all.seq
1651 TACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGA nem316_all.seq
1650 TACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGA a909_all.seq

TTAAAGGTTTGGCTTATGCAGTTGATGCCGAATGCAGAGGGTACAGCAGTA Majority

                3710        3720        3730        3740        3750
1698 TTAAAGGTTTGGCTTATGCAGTTGATGCCGAATGCAGAGGGTACAGCAGTA 2603_all.seq
1467 TTAAAGGTTTGGCTTATGCAGTTGATGCCGAATGCAGAGGGTACAGCAGTA 18rs21_all.seq
1699 TTAAAGGTTTGGCTTATGCAGTTGATGCCGAATGCAGAGGGTACAGCAGTA cohl_all.seq
1699 TTAAAGGTTTGGCTTATGCAGTTGATGCCGAATGCAGAGGGTACAGCAGTA cjb111_all.seq
1701 TTAAAGGTTTGGCTTATGCAGTTGATGCCGAATGCAGAGGGTACAGCAGTA nem316_all.seq
1700 TTAAAGGTTTGGCTTATGCAGTTGATGCCGAATGCAGAGGGTACAGCAGTA a909_all.seq

ACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGA Majority

                3760        3770        3780        3790        3800
1748 ACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGA 2603_all.seq
1517 ACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGA 18rs21_all.seq
1749 ACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGA cohl_all.seq
1749 ACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGA cjb111_all.seq
1751 ACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGA nem316_all.seq
1750 ACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGA a909_all.seq

TAAAGAAATCGAGTTTACAGTATCACAAACATCTTATAATACAAAACCAA Majority

                3810        3820        3830        3840        3850
1798 TAAAGAAATCGAGTTTACAGTATCACAAACATCTTATAATACAAAACCAA 2603_all.seq
1567 TAAAGAAATCGAGTTTACAGTATCACAAACATCTTATAATACAAAACCAA 18rs21_all.seq
1799 TAAAGAAATCGAGTTTACAGTATCACAAACATCTTATAATACAAAACCAA cohl_all.seq
1799 TAAAGAAATCGAGTTTACAGTATCACAAACATCTTATAATACAAAACCAA cjb111_all.seq
1801 TAAAGAAATCGAGTTTACAGTATCACAAACATCTTATAATACAAAACCAA nem316_all.seq
1800 TAAAGAAATCGAGTTTACAGTATCACAAACATCTTATAATACAAAACCAA a909_all.seq
```

FIGURE 18 J


Majority
2603_all.seq
18rs21_all.seq
coh1_all.seq
cjb111_all.seq
nem316_all.seq
a909_all.seq

FIGURE 18 K

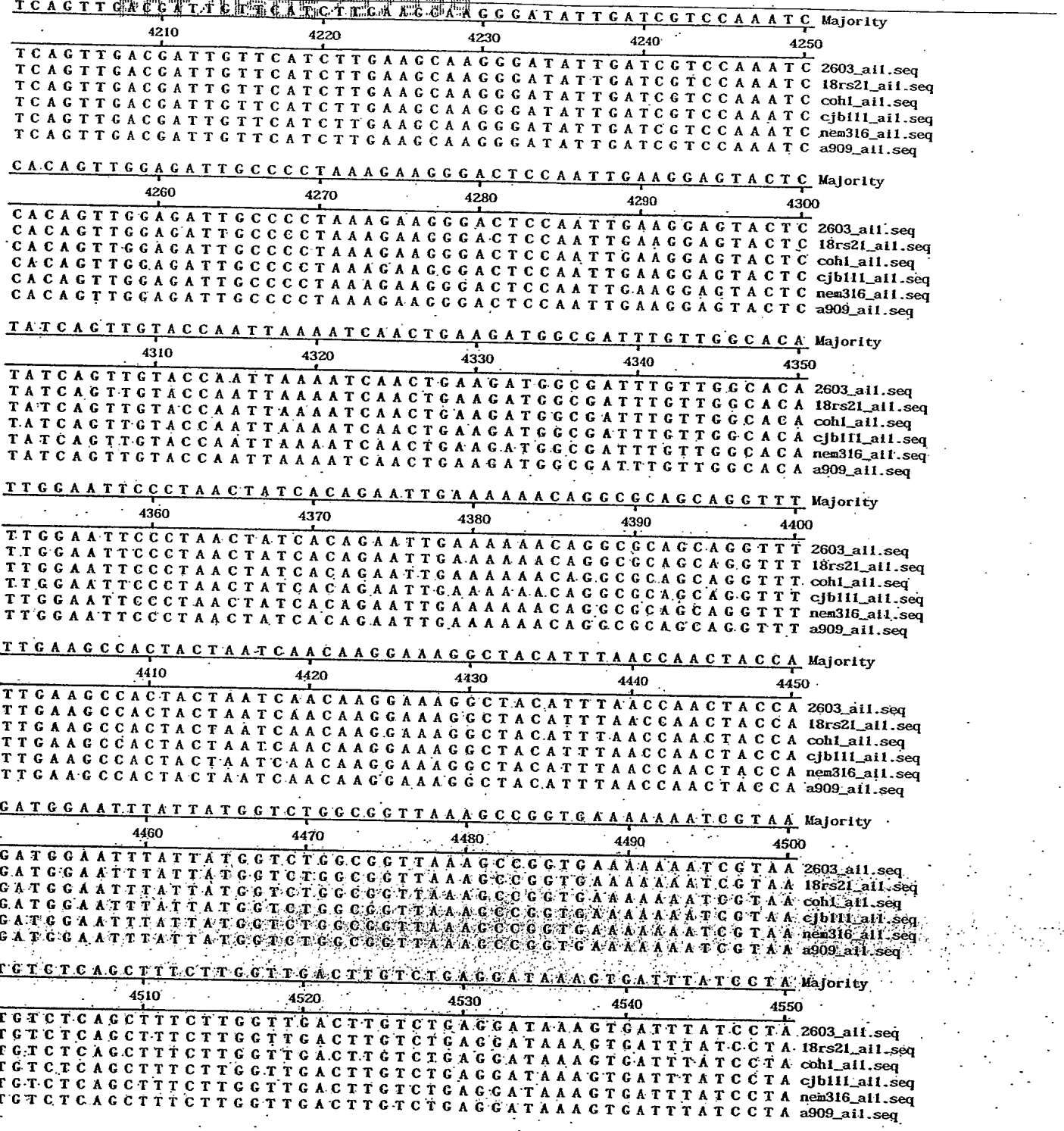
Majority
4210 4220 4230 4240 4250
4198 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC
3967 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC 2603_all.seq
4199 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC 18rs21_all.seq
4199 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC coh1_all.seq
4201 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC cjb111_all.seq
4200 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC nem316_all.seq
a909_all.seq
Majority
4260 4270 4280 4290 4300
4248 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC
4017 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC 2603_all.seq
4249 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC 18rs21_all.seq
4249 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC coh1_all.seq
4251 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC cjb111_all.seq
4250 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC nem316_all.seq
a909_all.seq
Majority
4310 4320 4330 4340 4350
4298 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA
4067 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA 2603_all.seq
4299 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA 18rs21_all.seq
4299 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA coh1_all.seq
4301 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA cjb111_all.seq
4300 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA nem316_all.seq
a909_all.seq
Majority
4360 4370 4380 4390 4400
4348 TTGGAATTCCCTAACTATCACAGAATTGAAAAAAACAGGCGCAGCAGGTTT
4117 TTGGAATTCCCTAACTATCACAGAATTGAAAAAAACAGGCGCAGCAGGTTT 2603_all.seq
4349 TTGGAATTCCCTAACTATCACAGAATTGAAAAAAACAGGCGCAGCAGGTTT 18rs21_all.seq
4349 TTGGAATTCCCTAACTATCACAGAATTGAAAAAAACAGGCGCAGCAGGTTT coh1_all.seq
4351 TTGGAATTCCCTAACTATCACAGAATTGAAAAAAACAGGCGCAGCAGGTTT cjb111_all.seq
4350 TTGGAATTCCCTAACTATCACAGAATTGAAAAAAACAGGCGCAGCAGGTTT nem316_all.seq
a909_all.seq
Majority
4410 4420 4430 4440 4450
4398 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA
4167 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA 2603_all.seq
4399 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA 18rs21_all.seq
4399 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA coh1_all.seq
4401 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA cjb111_all.seq
4400 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA nem316_all.seq
a909_all.seq
Majority
4460 4470 4480 4490 4500
4448 GATGGAATTTATTATGGTCTGGCGGTTAAAGCCGGTGAAAAAAATCGTAA
4217 GATGGAATTTATTATGGTCTGGCGGTTAAAGCCGGTGAAAAAAATCGTAA 2603_all.seq
4449 GATGGAATTTATTATGGTCTGGCGGTTAAAGCCGGTGAAAAAAATCGTAA 18rs21_all.seq
4449 GATGGAATTTATTATGGTCTGGCGGTTAAAGCCGGTGAAAAAAATCGTAA coh1_all.seq
4451 GATGGAATTTATTATGGTCTGGCGGTTAAAGCCGGTGAAAAAAATCGTAA cjb111_all.seq
4450 GATGGAATTTATTATGGTCTGGCGGTTAAAGCCGGTGAAAAAAATCGTAA nem316_all.seq
a909_all.seq
Majority
4510 4520 4530 4540 4550
4498 TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA
4267 TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA 2603_all.seq
4499 TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA 18rs21_all.seq
4499 TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA coh1_all.seq
4501 TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA cjb111_all.seq
4500 TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA nem316_all.seq
a909_all.seq

FIGURE 18 L

	AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT	Majority
	4560 4570 4580 4590 4600	
4548	AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT	2603_ail.seq
4317	AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT	18rs21_ail.seq
4549	AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT	cohl_ail.seq
4549	AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT	cjb111_ail.seq
4551	AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT	nem316_ail.seq
4550	AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT	a909_ail.seq
	GGTGATACCAAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAAA	Majority
	4610 4620 4630 4640 4650	
4598	GGTGATACCAAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAAA	2603_ail.seq
4367	GGTGATACCAAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAAA	18rs21_ail.seq
4599	GGTGATACCAAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAAA	cohl_ail.seq
4599	GGTGATACCAAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAAA	cjb111_ail.seq
4601	GGTGATACCAAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAAA	nem316_ail.seq
4600	GGTGATACCAAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAAA	a909_ail.seq
	GAATGGTAGGACTCCTATTCGTGTGAAAAATGGGGTGCATTCTCAAGATA	Majority
	4660 4670 4680 4690 4700	
4648	GAATGGTAGGACTCCTATTCGTGTGAAAAATGGGGTGCATTCTCAAGATA	2603_ail.seq
4417	GAATGGTAGGACTCCTATTCGTGTGAAAAATGGGGTGCATTCTCAAGATA	18rs21_ail.seq
4649	GAATGGTAGGACTCCTATTCGTGTGAAAAATGGGGTGCATTCTCAAGATA	cohl_ail.seq
4649	GAATGGTAGGACTCCTATTCGTGTGAAAAATGGGGTGCATTCTCAAGATA	cjb111_ail.seq
4651	GAATGGTAGGACTCCTATTCGTGTGAAAAATGGGGTGCATTCTCAAGATA	nem316_ail.seq
4650	GAATGGTAGGACTCCTATTCGTGTGAAAAATGGGGTGCATTCTCAAGATA	a909_ail.seq
	TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT	Majority
	4710 4720 4730 4740 4750	
4698	TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT	2603_ail.seq
4467	TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT	18rs21_ail.seq
4699	TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT	cohl_ail.seq
4699	TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT	cjb111_ail.seq
4701	TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT	nem316_ail.seq
4700	TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT	a909_ail.seq
	TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC	Majority
	4760 4770 4780 4790 4800	
4748	TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC	2603_ail.seq
4517	TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC	18rs21_ail.seq
4749	TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC	cohl_ail.seq
4749	TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC	cjb111_ail.seq
4751	TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC	nem316_ail.seq
4750	TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC	a909_ail.seq
	AGGATATCAGATCGGACAGGCAGAGACTGCTGTGACTATTGAAAAATCAA	Majority
	4810 4820 4830 4840 4850	
4798	AGGATATCAGATCGGACAGGCAGAGACTGCTGTGACTATTGAAAAATCAA	2603_ail.seq
4567	AGGATATCAGATCGGACAGGCAGAGACTGCTGTGACTATTGAAAAATCAA	18rs21_ail.seq
4799	AGGATATCAGATCGGACAGGCAGAGACTGCTGTGACTATTGAAAAATCAA	cohl_ail.seq
4799	AGGATATCAGATCGGACAGGCAGAGACTGCTGTGACTATTGAAAAATCAA	cjb111_ail.seq
4801	AGGATATCAGATCGGACAGGCAGAGACTGCTGTGACTATTGAAAAATCAA	nem316_ail.seq
4800	AGGATATCAGATCGGACAGGCAGAGACTGCTGTGACTATTGAAAAATCAA	a909_ail.seq
	AAACAGTAACAGTAACGATTGAAAATAAAAAAGTTCCGACACCTAAAGTG	Majority
	4860 4870 4880 4890 4900	
4848	AAACAGTAACAGTAACGATTGAAAATAAAAAAGTTCCGACACCTAAAGTG	2603_ail.seq
4617	AAACAGTAACAGTAACGATTGAAAATAAAAAAGTTCCGACACCTAAAGTG	18rs21_ail.seq
4849	AAACAGTAACAGTAACGATTGAAAATAAAAAAGTTCCGACACCTAAAGTG	cohl_ail.seq
4849	AAACAGTAACAGTAACGATTGAAAATAAAAAAGTTCCGACACCTAAAGTG	cjb111_ail.seq
4851	AAACAGTAACAGTAACGATTGAAAATAAAAAAGTTCCGACACCTAAAGTG	nem316_ail.seq
4850	AAACAGTAACAGTAACGATTGAAAATAAAAAAGTTCCGACACCTAAAGTG	a909_ail.seq

FIGURE 18 M

```
     CCATCTCGAGGAGCTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC Majority
              4910      4920      4930      4940      4950
4898 CCATCTCGAGGAGCTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC 2603_ai1.seq
4667 CCATCTCGAGGAGCTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC 18rs21_ai1.seq
4899 CCATCTCGAGGAGCTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC coh1_ai1.seq
4899 CCATCTCGAGGAGCTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC cjb111_ai1.seq
4901 CCATCTCGAGGAGCTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC nem316_ai1.seq
4900 CCATCTCGAGGAGCTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC a909_ai1.seq

     ACTTGTAATTATTGGTGGTATTTTAATTGCTTTAGCCTTACGATTACTAT Majority
              4960      4970      4980      4990      5000
4948 ACTTGTAATTATTGGTGGTATTTTAATTGCTTTAGCCTTACGATTACTAT 2603_ai1.seq
4717 ACTTGTAATTATTGGTGGTATTTTAATTGCTTTAGCCTTACGATTACTAT 18rs21_ai1.seq
4949 ACTTGTAATTATTGGTGGTATTTTAATTGCTTTAGCCTTACGATTACTAT coh1_ai1.seq
4949 ACTTGTAATTATTGGTGGTATTTTAATTGCTTTAGCCTTACGATTACTAT cjb111_ai1.seq
4951 ACTTGTAATTATTGGTGGTATTTTAATTGCTTTAGCCTTACGATTACTAT nem316_ai1.seq
4950 ACTTGTAATTATTGGTGGTATTTTAATTGCTTTAGCCTTACGATTACTAT a909_ai1.seq

     CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA Majority
              5010      5020      5030      5040      5050
4998 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA 2603_ai1.seq
4767 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA 18rs21_ai1.seq
4999 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA coh1_ai1.seq
4999 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA cjb111_ai1.seq
5001 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA nem316_ai1.seq
5000 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA a909_ai1.seq

     AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT Majority
              5060      5070      5080      5090      5100
5048 AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT 2603_ai1.seq
4817 AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT 18rs21_ai1.seq
5049 AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT coh1_ai1.seq
5049 AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT cjb111_ai1.seq
5051 AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT nem316_ai1.seq
5050 AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT a909_ai1.seq

     TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC Majority
              5110      5120      5130      5140      5150
5098 TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC 2603_ai1.seq
4867 TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC 18rs21_ai1.seq
5099 TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC coh1_ai1.seq
5099 TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC cjb111_ai1.seq
5101 TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC nem316_ai1.seq
5100 TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC a909_ai1.seq

     TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA Majority
              5160      5170      5180      5190      5200
5148 TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA 2603_ai1.seq
4917 TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA 18rs21_ai1.seq
5149 TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA coh1_ai1.seq
5149 TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA cjb111_ai1.seq
5151 TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA nem316_ai1.seq
5150 TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA a909_ai1.seq

     GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA Majority
              5210      5220      5230      5240      5250
5198 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA 2603_ai1.seq
4967 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA 18rs21_ai1.seq
5199 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA coh1_ai1.seq
5199 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA cjb111_ai1.seq
5201 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA nem316_ai1.seq
5200 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA a909_ai1.seq
```

FIGURE 18 N

```
                ACGCCAGTATAGCAGGTGCCAAAACTAATGGCGAATATCCAGCGCTTAAA Majority
                         5260      5270      5280      5290      5300
5248 ACGCCAGTATAGCAGGTGCCAAAACTAATGGCGAATATCCAGCGCTTAAA 2603_all.seq
5017 ACGCCAGTATAGCAGGTGCCAAAACTAATGGCGAATATCCAGCGCTTAAA 18rs21_all.seq
5249 ACGCCAGTATAGCAGGTGCCAAAACTAATGGCGAATATCCAGCGCTTAAA cohl_all.seq
5249 ACGCCAGTATAGCAGGTGCCAAAACTAATGGCGAATATCCAGCGCTTAAA cjb111_all.seq
5251 ACGCCAGTATAGCACGTGCCAAAACTAATGGCGAATATTCAGCGCTTAAA nem316_all.seq
5250 ACGCCAGTATAGCAGGTGCCAAAACTAATGGCGAATATCCAGCGCTTAAA a909_all.seq

                GACCCCTACTCTGCTGAACAAAAGCAGGCAGGGGTCGTTGAGTACGCCCG Majority
                         5310      5320      5330      5340      5350
5298 GACCCCTACTCTGCTGAACAAAAGCAGGCAGGGGTCGTTGAGTACGCCCG 2603_all.seq
5067 GACCCCTACTCTGCTGAACAAAAGCAGGCAGGGGTCGTTGAGTACGCCCG 18rs21_all.seq
5299 GACCCCTACTCTGCTGAACAAAAGCAGGCAGGGGTCGTTGAGTACGCCCG cohl_all.seq
5299 GACCCCTACTCTGCTGAACAAAAGCAGGCAGGGGTCGTTGAGTACGCCCG cjb111_all.seq
5301 GACCCCTACTCTGCTGAACAAAAGCAGGCAGGGGTCGTTGAGTACGCCCG nem316_all.seq
5300 GACCCCTACTCTGCTGAACAAAAGCAGGCAGGGGTCGTTGAGTACGCCCG a909_all.seq

                CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA Majority
                         5360      5370      5380      5390      5400
5348 CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA 2603_all.seq
5117 CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA 18rs21_all.seq
5349 CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA cohl_all.seq
5349 CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA cjb111_all.seq
5351 CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA nem316_all.seq
5350 CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA a909_all.seq

                ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAAATCTTCAGAGG Majority
                         5410      5420      5430      5440      5450
5398 ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAAATCTTCAGAGG 2603_all.seq
5167 ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAAATCTTCAGAGG 18rs21_all.seq
5399 ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAAATCTTCAGAGG cohl_all.seq
5399 ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAAATCTTCAGAGG cjb111_all.seq
5401 ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAAATCTTCAGAGG nem316_all.seq
5400 ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAAATCTTCAGAGG a909_all.seq

                GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC Majority
                         5460      5470      5480      5490      5500
448 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC 2603_all.seq
217 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC 18rs21_all.seq
449 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC cohl_all.seq
449 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC cjb111_all.seq
451 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC nem316_all.seq
450 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC a909_all.seq

                TCATGCCGTTCTAACTGCCCATCGAGGGCTACCAACGGCCAAGCTATTTA Majority
                         5510      5520      5530      5540      5550
498 TCATGCCGTTCTAACTGCCCATCGAGGGCTACCAACGGCCAAGCTATTTA 2603_all.seq
267 TCATGCCGTTCTAACTGCCCATCGAGGGCTACCAACGGCCAAGCTATTTA 18rs21_all.seq
499 TCATGCCGTTCTAACTGCCCATCGAGGGCTACCAACGGCCAAGCTATTTA cohl_all.seq
499 TCATGCCGTTCTAACTGCCCATCGAGGGCTACCAACGGCCAAGCTATTTA cjb111_all.seq
501 TCATGCCGTTCTAACTGCCCATCGAGGGCTACCAACGGCCAAGCTATTTA nem316_all.seq
500 TCATGCCGTTCTAACTGCCCATCGAGGGCTACCAACGGCCAAGCTATTTA a909_all.seq

                CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATC Majority
                         5560      5570      5580      5590      5600
548 CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATC 2603_all.seq
317 CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATC 18rs21_all.seq
549 CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATC cohl_all.seq
549 CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATC cjb111_all.seq
551 CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATC nem316_all.seq
550 CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATC a909_all.seq
```

FIGURE 18 O

```
      GGCGGAATGATTGCTTATCAGGTAGACCAAATCAAAGTTATCGCCCCTGA Majority

                5610        5620        5630        5640        5650
598   GGCGGAAAGATTGCTTATCAGGTAGACCAAATCAAAGTTATCGCCCCTGA 2603_all.seq
367   GGCGGAAAGATTGCTTATCAGGTAGACCAAATCAAAGTTATCGCCCCTGA 18rs21_all.seq
599   GGCGGAAAGATTGCTTATCAGGTAGACCAAATCAAAGTTATCGCCCCTGA cohl_all.seq
599   GGCGGAAAGATTGCTTATCAGGTAGACCAAATCAAAGTTATCGCCCCTGA cjb111_all.seq
601   GGCGGAAAGATTGCTTATCAGGTAGACCAAATCAAAGTTATCGCCCCTGA nem316_all.seq
600   GGCGGAAAGATTGCTTATCAGGTAGACCAAATCAAAGTTATCGCCCCTGA a909_all.seq

      TCAGTTAGAGGATTTGTACGTGATTCAAGGAGAAGATCACGTCACCCTAT Majority

                5660        5670        5680        5690        5700
648   TCAGTTAGAGGATTTGTACGTGATTCAAGGAGAAGATCACGTCACCCTAT 2603_all.seq
417   TCAGTTAGAGGATTTGTACGTGATTCAAGGAGAAGATCACGTCACCCTAT 18rs21_all.seq
649   TCAGTTAGAGGATTTGTACGTGATTCAAGGAGAAGATCACGTCACCCTAT cohl_all.seq
649   TCAGTTAGAGGATTTGTACGTGATTCAAGGAGAAGATCACGTCACCCTAT cjb111_all.seq
651   TCAGTTAGAGGATTTGTACGTGATTCAAGGAGAAGATCACGTCACCCTAT nem316_all.seq
650   TCAGTTAGAGGATTTGTACGTGATTCAAGGAGAAGATCACGTCACCCTAT a909_all.seq

      TAACTTGCACACCTTATATGATAAATAGTCATCGCCTCCTCGTTCGAGGC Majority

                5710        5720        5730        5740        5750
698   TAACTTGCACACCTTATATGATAAATAGTCATCGCCTCCTCGTTCGAGGC 2603_all.seq
467   TAACTTGCACACCTTATATGATAAATAGTCATCGCCTCCTCGTTCGAGGC 18rs21_all.seq
699   TAACTTGCACACCTTATATGATAAATAGTCATCGCCTCCTCGTTCGAGGC cohl_all.seq
699   TAACTTGCACACCTTATATGATAAATAGTCATCGCCTCCTCGTTCGAGGC cjb111_all.seq
701   TAACTTGCACACCTTATATGATAAATAGTCATCGCCTCCTCGTTCGAGGC nem316_all.seq
700   TAACTTGCACACCTTATATGATAAATAGTCATCGCCTCCTCGTTCGAGGC a909_all.seq

      AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT Majority

                5760        5770        5780        5790        5800
748   AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT 2603_all.seq
517   AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT 18rs21_all.seq
749   AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT cohl_all.seq
749   AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT cjb111_all.seq
751   AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT nem316_all.seq
750   AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT a909_all.seq

      CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA Majority

                5810        5820        5830        5840        5850
798   CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA 2603_all.seq
567   CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA 18rs21_all.seq
799   CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA cohl_all.seq
799   CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA cjb111_all.seq
801   CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA nem316_all.seq
800   CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA a909_all.seq

      TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGACGAAACAGAAAAAGCGG Majority

                5860        5870        5880        5890        5900
848   TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGACGAAACAGAAAAAGCGG 2603_all.seq
617   TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGACGAAACAGAAAAAGCGG 18rs21_all.seq
849   TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGACGAAACAGAAAAAGCGG cohl_all.seq
849   TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGACGAAACAGAAAAAGCGG cjb111_all.seq
851   TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGACGAAACAGAAAAAGCGG nem316_all.seq
850   TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGACGAAACAGAAAAAGCGG a909_all.seq

      AGAAAGAATGAAAAAGCGGCTAGTCAAAATAGTCACAATAATTCGAAATA Majority

                5910        5920        5930        5940        5950
898   AGAAAGAATGAAAAAGCGGCTAGTCAAAATAGTCACAATAATTCGAAATA 2603_all.seq
667   AGAAAGAATGAAAAAGCGGCTAGTCAAAATAGTCACAATAATTCGAAATA 18rs21_all.seq
899   AGAAAGAATGAAAAAGCGGCTAGTCAAAATAGTCACAATAATTCGAAATA cohl_all.seq
899   AGAAAGAATGAAAAAGCGGCTAGTCAAAATAGTCACAATAATTCGAAATA cjb111_all.seq
901   AGAAAGAATGAAAAAGCGGCTAGTCAAAATAGTCACAATAATTCGAAATA nem316_all.seq
900   AGAAAGAATGAAAAAGCGGCTAGTCAAAATAGTCACAATAATTCGAAATA a909_all.seq
```

FIGURE 18 P

```
     ATAAAATCAGAACCCTCATTTTTGTGATGGGAAGTCTGATTCTCTTATTT Majority
                5960      5970      5980      5990      6000
5948 ATAAAATCAGAACCCTCATTTTTGTGATGGGAAGTCTGATTCTCTTATTT 2603_all.seq
5717 ATAAAATCAGAACCCTCATTTTTGTGATGGGAAGTCTGATTCTCTTATTT 18rs21_all.seq
5949 ATAAAATCAGAACCCTCATTTTTGTGATGGGAAGTCTGATTCTCTTATTT coh1_all.seq
5949 ATAAAATCAGAACCCTCATTTTTGTGATGGGAAGTCTGATTCTCTTATTT cjb111_all.seq
5951 ATAAAATCAGAACCCTCATTTTTGTGATGGGAAGTCTGATTCTCTTATTT nem316_all.seq
5950 ATAAAATCAGAACCCTCATTTTTGTGATGGGAAGTCTGATTCTCTTATTT a909_all.seq

     CCGATTGTGAGCCAGGTAAGTTACTACCTTGCTTCGCATCAAAATATTAA Majority
                6010      6020      6030      6040      6050
5998 CCGATTGTGAGCCAGGTAAGTTACTACCTTGCTTCGCATCAAAATATTAA 2603_all.seq
5767 CCGATTGTGAGCCAGGTAAGTTACTACCTTGCTTCGCATCAAAATATTAA 18rs21_all.seq
5999 CCGATTGTGAGCCAGGTAAGTTACTACCTTGCTTCGCATCAAAATATTAA coh1_all.seq
5999 CCGATTGTGAGCCAGGTAAGTTACTACCTTGCTTCGCATCAAAATATTAA cjb111_all.seq
6001 CCGATTGTGAGCCAGGTAAGTTACTACCTTGCTTCGCATCAAAATATTAA nem316_all.seq
6000 CCGATTGTGAGCCAGGTAAGTTACTACCTTGCTTCGCATCAAAATATTAA a909_all.seq

     TCAATTTAAGCGGGAAGTCGCTAAGATTGATACTAATACGGTTGAACGAC Majority
                6060      6070      6080      6090      6100
6048 TCAATTTAAGCGGGAAGTCGCTAAGATTGATACTAATACGGTTGAACGAC 2603_all.seq
5817 TCAATTTAAGCGGGAAGTCGCTAAGATTGATACTAATACGGTTGAACGAC 18rs21_all.seq
6049 TCAATTTAAGCGGGAAGTCGCTAAGATTGATACTAATACGGTTGAACGAC coh1_all.seq
6049 TCAATTTAAGCGGGAAGTCGCTAAGATTGATACTAATACGGTTGAACGAC cjb111_all.seq
6051 TCAATTTAAGCGGGAAGTCGCTAAGATTGATACTAATACGGTTGAACGAC nem316_all.seq
6050 TCAATTTAAGCGGGAAGTCGCTAAGATTGATACTAATACGGTTGAACGAC a909_all.seq

     GCATCGCTTTAGCTAATGCTTACAATGAGACGTTATCAAGGAATCCCTTG Majority
                6110      6120      6130      6140      6150
6098 GCATCGCTTTAGCTAATGCTTACAATGAGACGTTATCAAGGAATCCCTTG 2603_all.seq
5867 GCATCGCTTTAGCTAATGCTTACAATGAGACGTTATCAAGGAATCCCTTG 18rs21_all.seq
6099 GCATCGCTTTAGCTAATGCTTACAATGAGACGTTATCAAGGAATCCCTTG coh1_all.seq
6099 GCATCGCTTTAGCTAATGCTTACAATGAGACGTTATCAAGGAATCCCTTG cjb111_all.seq
6101 GCATCGCTTTAGCTAATGCTTACAATGAGACGTTATCAAGGAATCCCTTG nem316_all.seq
6100 GCATCGCTTTAGCTAATGCTTACAATGAGACGTTATCAAGGAATCCCTTG a909_all.seq

     CTTATAGACCCTTTTACCAGTAAGCAAAAAGAAGGTTTGAGAGAGTATGC Majority
                6160      6170      6180      6190      6200
6148 CTTATAGACCCTTTTACCAGTAAGCAAAAAGAAGGTTTGAGAGAGTATGC 2603_all.seq
5917 CTTATAGACCCTTTTACCAGTAAGCAAAAAGAAGGTTTGAGAGAGTATGC 18rs21_all.seq
6149 CTTATAGACCCTTTTACCAGTAAGCAAAAAGAAGGTTTGAGAGAGTATGC coh1_all.seq
6149 CTTATAGACCCTTTTACCAGTAAGCAAAAAGAAGGTTTGAGAGAGTATGC cjb111_all.seq
6151 CTTATAGACCCTTTTACCAGTAAGCAAAAAGAAGGTTTGAGAGAGTATGC nem316_all.seq
6150 CTTATAGACCCTTTTACCAGTAAGCAAAAAGAAGGTTTGAGAGAGTATGC a909_all.seq

     TCGTATGCTTGAAGTTCATGAGCAAATAGGTCATGTGGCAATCCCAAGTA Majority
                6210      6220      6230      6240      6250
6198 TCGTATGCTTGAAGTTCATGAGCAAATAGGTCATGTGGCAATCCCAAGTA 2603_all.seq
5967 TCGTATGCTTGAAGTTCATGAGCAAATAGGTCATGTGGCAATCCCAAGTA 18rs21_all.seq
6199 TCGTATGCTTGAAGTTCATGAGCAAATAGGTCATGTGGCAATCCCAAGTA coh1_all.seq
6199 TCGTATGCTTGAAGTTCATGAGCAAATAGGTCATGTGGCAATCCCAAGTA cjb111_all.seq
6201 TCGTATGCTTGAAGTTCATGAGCAAATAGGTCATGTGGCAATCCCAAGTA nem316_all.seq
6200 TCGTATGCTTGAAGTTCATGAGCAAATAGGTCATGTGGCAATCCCAAGTA a909_all.seq

     TTGCGGTTGATATTCCAATTTATGCTGGAACATCCGAAACTGTGCTTCAG Majority
                6260      6270      6280      6290      6300
6248 TTGCGGTTGATATTCCAATTTATGCTGGAACATCCGAAACTGTGCTTCAG 2603_all.seq
6017 TTGCGGTTGATATTCCAATTTATGCTGGAACATCCGAAACTGTGCTTCAG 18rs21_all.seq
6249 TTGCGGTTGATATTCCAATTTATGCTGGAACATCCGAAACTGTGCTTCAG coh1_all.seq
6249 TTGCGGTTGATATTCCAATTTATGCTGGAACATCCGAAACTGTGCTTCAG cjb111_all.seq
6251 TTGCGGTTGATATTCCAATTTATGCTGGAACATCCGAAACTGTGCTTCAG nem316_all.seq
6250 TTGCGGTTGATATTCCAATTTATGCTGGAACATCCGAAACTGTGCTTCAG a909_all.seq
```

FIGURE 18 Q

```
AAAGGTACTGCGCGATTTGCAGCGAACCGACTCTTCCAGTGCGAGGTTTGTC Majority
                6310        6320        6330        6340        6350
6298 AAAGGTAGTGGCCATTTGGAGCGAACCAGTCTTCCAGTGCGAGGTTTGTC 2603_all.seq
6067 AAAGGTAGTGGCCATTTGGAGCGAACCAGTCTTCCAGTGCGAGGTTTGTC 18rs21_all.seq
6299 AAAGGTAGTGGCCATTTGGAGCGAACCAGTCTTCCAGTGCGAGGTTTGTC cohl_all.seq
6299 AAAGGTAGTGGCCATTTGGAGCGAACCAGTCTTCCAGTGCGAGGTTTGTC cjb111_all.seq
6301 AAAGGTAGTGGCCATTTGGAGCGAACCAGTCTTCCAGTGCGAGGTTTGTC nem316_all.seq
6300 AAAGGTAGTGGCCATTTGGAGCGAACCAGTCTTCCAGTGCGAGGTTTGTC a909_all.seq

AACCCATTCAGTACTAACTGCCCACCGTGCCTTGCCAACAGCTAGGCTAT Majority
                6360        6370        6380        6390        6400
6348 AACCCATTCAGTACTAACTGCCCACCGTGCCTTGCCAACAGCTAGGCTAT 2603_all.seq
6117 AACCCATTCAGTACTAACTGCCCACCGTGCCTTGCCAACAGCTAGGCTAT 18rs21_all.seq
6349 AACCCATTCAGTACTAACTGCCCACCGTGCCTTGCCAACAGCTAGGCTAT cohl_all.seq
6349 AACCCATTCAGTACTAACTGCCCACCGTGCCTTGCCAACAGCTAGGCTAT cjb111_all.seq
6351 AACCCATTCAGTACTAACTGCCCACCGTGCCTTGCCAACAGCTAGGCTAT nem316_all.seq
6350 AACCCATTCAGTACTAACTGCCCACCGTGCCTTGCCAACAGCTAGGCTAT a909_all.seq

TTACCGACTTAAATAAAGTTAAAAAAAGGCCAGATTTTCTATGTGACGAAC Majority
                6410        6420        6430        6440        6450
6398 TTACCGACTTAAATAAAGTTAAAAAAAGGCCAGATTTTCTATGTGACGAAC 2603_all.seq
6167 TTACCGACTTAAATAAAGTTAAAAAAAGGCCAGATTTTCTATGTGACGAAC 18rs21_all.seq
6399 TTACCGACTTAAATAAAGTTAAAAAAAGGCCAGATTTTCTATGTGACGAAC cohl_all.seq
6399 TTACCGACTTAAATAAAGTTAAAAAAAGGCCAGATTTTCTATGTGACGAAC cjb111_all.seq
6401 TTACCGACTTAAATAAAGTTAAAAAAAGGCCAGATTTTCTATGTGACGAAC nem316_all.seq
6400 TTACCGACTTAAATAAAGTTAAAAAAAGGCCAGATTTTCTATGTGACGAAC a909_all.seq

ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC Majority
                6460        6470        6480        6490        6500
6448 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC 2603_all.seq
6217 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC 18rs21_all.seq
6449 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC cohl_all.seq
6449 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC cjb111_all.seq
6451 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC nem316_all.seq
6450 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC a909_all.seq

AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT Majority
                6510        6520        6530        6540        6550
6498 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT 2603_all.seq
6267 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT 18rs21_all.seq
6499 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT cohl_all.seq
6499 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT cjb111_all.seq
6501 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT nem316_all.seq
6500 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT a909_all.seq

TGCTGACTTGCACACCTTACATGATCAATAGTCATCGTCTCTTGGTAAAA Majority
                6560        6570        6580        6590        6600
6548 TGCTGACTTGCACACCTTACATGATCAATAGTCATCGTCTCTTGGTAAAA 2603_all.seq
6317 TGCTGACTTGCACACCTTACATGATCAATAGTCATCGTCTCTTGGTAAAA 18rs21_all.seq
6549 TGCTGACTTGCACACCTTACATGATCAATAGTCATCGTCTCTTGGTAAAA cohl_all.seq
6549 TGCTGACTTGCACACCTTACATGATCAATAGTCATCGTCTCTTGGTAAAA cjb111_all.seq
6551 TGCTGACTTGCACACCTTACATGATCAATAGTCATCGTCTCTTGGTAAAA nem316_all.seq
6550 TGCTGACTTGCACACCTTACATGATCAATAGTCATCGTCTCTTGGTAAAA a909_all.seq

GGAGAGCGTATTCCTTATGATTCTACCGAGCCGGAAAAGCACAAAGAACA Majority
                6610        6620        6630        6640        6650
6598 GGAGAGCGTATTCCTTATGATTCTACCGAGCCGGAAAAGCACAAAGAACA 2603_all.seq
6367 GGAGAGCGTATTCCTTATGATTCTACCGAGCCGGAAAAGCACAAAGAACA 18rs21_all.seq
6599 GGAGAGCGTATTCCTTATGATTCTACCGAGCCGGAAAAGCACAAAGAACA cohl_all.seq
6599 GGAGAGCGTATTCCTTATGATTCTACCGAGCCGGAAAAGCACAAAGAACA cjb111_all.seq
6601 GGAGAGCGTATTCCTTATGATTCTACCGAGCCGGAAAAGCACAAAGAACA nem316_all.seq
6600 GGAGAGCGTATTCCTTATGATTCTACCGAGCCGGAAAAGCACAAAGAACA a909_all.seq
```

FIGURE 18 R

```
      AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTACTAGTAT Majority
              6660      6670      6680      6690      6700
6648  AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTACTAGTAT 2603_all.seq
6417  AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTACTAGTAT 18rs21_all.seq
6649  AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTACTAGTAT coh1_all.seq
6649  AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTACTAGTAT cjb111_all.seq
6651  AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTACTAGTAT nem316_all.seq
6650  AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTACTAGTAT a909_all.seq

      TATTAATTGGACTCTTCATCGTGATAATGATGAGAAGATGGATGCAACAT Majority
              6710      6720      6730      6740      6750
6698  TATTAATTGGACTCTTCATCGTGATAATGATGAGAAGATGGATGCAACAT 2603_all.seq
6467  TATTAATTGGACTCTTCATCGTGATAATGATGAGAAGATGGATGCAACAT 18rs21_all.seq
6699  TATTAATTGGACTCTTCATCGTGATAATGATGAGAAGATGGATGCAACAT coh1_all.seq
6699  TATTAATTGGACTCTTCATCGTGATAATGATGAGAAGATGGATGCAACAT cjb111_all.seq
6701  TATTAATTGGACTCTTCATCGTGATAATGATGAGAAGATGGATGCAACAT nem316_all.seq
6700  TATTAATTGGACTCTTCATCGTGATAATGATGAGAAGATGGATGCAACAT a909_all.seq

      CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT Majority
              6760      6770      6780      6790      6800
6748  CGTCAATAACGATGTTGTGAATGGCTTACTT----ATCAAATAGGTGACT 2603_all.seq
6517  CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT 18rs21_all.seq
6749  CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT coh1_all.seq
6749  CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT cjb111_all.seq
6751  CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT nem316_all.seq
6750  CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT a909_all.seq

      AATGATGATTGTGAATAATGGTTATCTAGAAGGGAGAAAAATGAAAAAGA Majority
              6810      6820      6830      6840      6850
6794  AATGATGATTGTGAATAATGGTTATCTAGAAGGGAGAAAAATGAAAAAGA 2603_all.seq
6567  AATGATGATTGTGAATAATGGTTATCTAGAAGGGAGAAAAATGAAAAAGA 18rs21_all.seq
6799  AATGATGATTGTGAATAATGGTTATCTAGAAGGGAGAAAAATGAAAAAGA coh1_all.seq
6799  AATGATGATTGTGAATAATGGTTATCTAGAAGGGAGAAAAATGAAAAAGA cjb111_all.seq
6801  AATGATGATTGTGAATAATGGTTATCTAGAAGGGAGAAAAATGAAAAAGA nem316_all.seq
6800  AATGATGATTGTGAATAATGGTTATCTAGAAGGGAGAAAAATGAAAAAGA a909_all.seq

      GACAAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAA Majority
              6860      6870      6880      6890      6900
6844  GACAAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAA 2603_all.seq
6617  GACAAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAA 18rs21_all.seq
6849  GACAAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAA coh1_all.seq
6849  GACAAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAA cjb111_all.seq
6851  GACAAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAA nem316_all.seq
6850  GACAAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAA a909_all.seq

      ATTCCATTTGGTATATTGGTACAAGGTGAAACCCAAGATACCAATCAAGC Majority
              6910      6920      6930      6940      6950
6894  ATTCCATTTGGTATATTGGTACAAGGTGAAACCCAAGATACCAATCAAGC 2603_all.seq
6667  ATTCCATTTGGTATATTGGTACAAGGTGAAACCCAAGATACCAATCAAGC 18rs21_all.seq
6899  ATTCCATTTGGTATATTGGTACAAGGTGAAACCCAAGATACCAATCAAGC coh1_all.seq
6899  ATTCCATTTGGTATATTGGTACAAGGTGAAACCCAAGATACCAATCAAGC cjb111_all.seq
6901  ATTCCATTTGGTATATTGGTACAAGGTGAAACCCAAGATACCAATCAAGC nem316_all.seq
6900  ATTCCATTTGGTATATTGGTACAAGGTGAAACCCAAGATACCAATCAAGC a909_all.seq

      ACTTGGAAAAGTAATTGTTAAAAAAAACGGGAGACAATGCTACACCATTAG Majority
              6960      6970      6980      6990      7000
6944  ACTTGGAAAAGTAATTGTTAAAAAAAACGGGAGACAATGCTACACCATTAG 2603_all.seq
6717  ACTTGGAAAAGTAATTGTTAAAAAAAACGGGAGACAATGCTACACCATTAG 18rs21_all.seq
6949  ACTTGGAAAAGTAATTGTTAAAAAAAACGGGAGACAATGCTACACCATTAG coh1_all.seq
6949  ACTTGGAAAAGTAATTGTTAAAAAAAACGGGAGACAATGCTACACCATTAG cjb111_all.seq
6951  ACTTGGAAAAGTAATTGTTAAAAAAAACGGGAGACAATGCTACACCATTAG nem316_all.seq
6950  ACTTGGAAAAGTAATTGTTAAAAAAAACGGGGGACAATGCTACACCATTAG a909_all.seq
```

FIGURE 18 S

```
GCAAAGCGACTTTTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGT Majority

          7010      7020      7030      7040      7050
6994 GCAAAGCGACTTTTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGT 2603_all.seq
5767 GCAAAGCGACTTTTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGT 18rs21_all.seq
6999 GCAAAGCGACTTTTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGT cohl_all.seq
6999 GCAAAGCGACTTTTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGT cjbill_all.seq
7001 GCAAAGCGACTTTTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGT nem316_all.seq
7000 GCAAAGCGACTTTTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGT a909_all.seq

CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC Majority

          7060      7070      7080      7090      7100
7044 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC 2603_all.seq
6817 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC 18rs21_all.seq
7049 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC cohl_all.seq
7049 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC cjbill_all.seq
7051 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC nem316_all.seq
7050 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC a909_all.seq

TGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAA Majority

          7110      7120      7130      7140      7150
7094 TGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAA 2603_all.seq
6867 TGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAA 18rs21_all.seq
7099 TGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAA cohl_all.seq
7099 TGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAA cjbill_all.seq
7101 TGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAA nem316_all.seq
7100 TGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAA a909_all.seq

CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC Majority

          7160      7170      7180      7190      7200
7144 CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC 2603_all.seq
6917 CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC 18rs21_all.seq
7149 CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC cohl_all.seq
7149 CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC cjbill_all.seq
7151 CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC nem316_all.seq
7150 CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC a909_all.seq

GAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGC Majority

          7210      7220      7230      7240      7250
7194 GAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGC 2603_all.seq
6967 GAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGC 18rs21_all.seq
7199 GAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGC cohl_all.seq
7199 GAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGC cjbill_all.seq
7201 GAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGC nem316_all.seq
7200 GAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGC a909_all.seq

CCAATATCCAAAATCAGCTATTTATGAGGATACAAAAGAAAATTACCCAT Majority

          7260      7270      7280      7290      7300
7244 CCAATATCCAAAATCAGCTATTTATGAGGATACAAAAGAAAATTACCCAT 2603_all.seq
7017 CCAATATCCAAAATCAGCTATTTATGAGGATACAAAAGAAAATTACCCAT 18rs21_all.seq
7249 CCAATATCCAAAATCAGCTATTTATGAGGATACAAAAGAAAATTACCCAT cohl_all.seq
7249 CCAATATCCAAAATCAGCTATTTATGAGGATACAAAAGAAAATTACCCAT cjbill_all.seq
7251 CCAATATCCAAAATCAGCTATTTATGAGGATACAAAAGAAAATTACCCAT nem316_all.seq
7250 CCAATATCCAAAATCAGCTATTTATGAGGATACAAAAGAAAATTACCCAT a909_all.seq

TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT Majority

          7310      7320      7330      7340      7350
7294 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT 2603_all.seq
7067 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT 18rs21_all.seq
7299 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT cohl_all.seq
7299 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT cjbill_all.seq
7301 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT nem316_all.seq
7300 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT a909_all.seq
```

FIGURE 18T

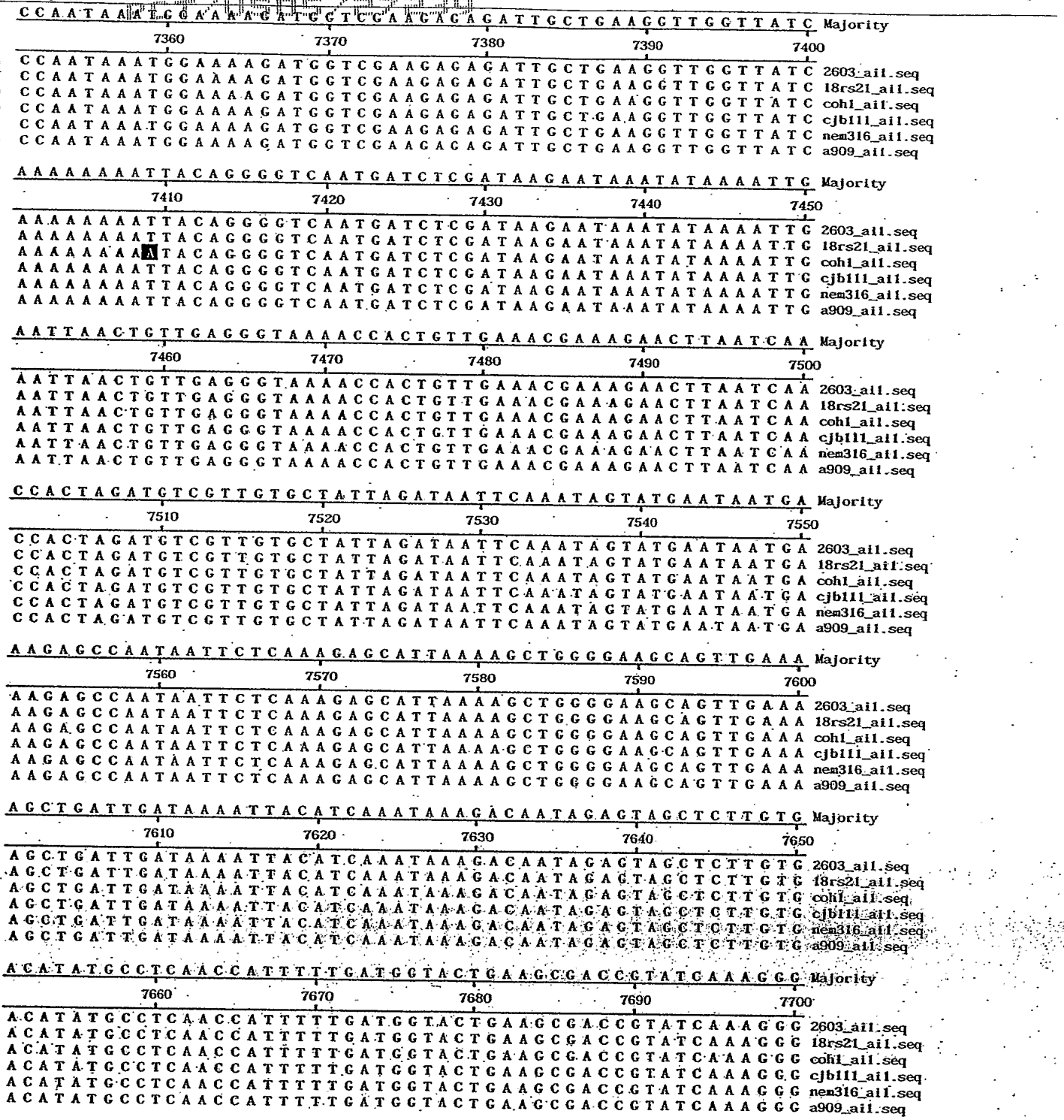
CCAATAAATGGAAAAGATGGTCGAAGAGAGATTGCTGAAGGTTGGTTATC Majority
7360 7370 7380 7390 7400
7344 CCAATAAATGGAAAAGATGGTCGAAGAGAGATTGCTGAAGGTTGGTTATC 2603_all.seq
7117 CCAATAAATGGAAAAGATGGTCGAAGAGAGATTGCTGAAGGTTGGTTATC 18rs21_all.seq
7349 CCAATAAATGGAAAAGATGGTCGAAGAGAGATTGCTGAAGGTTGGTTATC cohl_all.seq
7349 CCAATAAATGGAAAAGATGGTCGAAGAGAGATTGCTGAAGGTTGGTTATC cjb111_all.seq
7351 CCAATAAATGGAAAAGATGGTCGAAGAGAGATTGCTGAAGGTTGGTTATC nem316_all.seq
7350 CCAATAAATGGAAAAGATGGTCGAAGACACAGATTGCTGAAGGTTGGTTATC a909_all.seq
AAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATATAAAATTG Majority
7410 7420 7430 7440 7450
7394 AAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATATAAAATTG 2603_all.seq
7167 AAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATATAAAATTG 18rs21_all.seq
7399 AAAAAAAAATACAGGGGTCAATGATCTCGATAAGAATAAATATAAAATTG cohl_all.seq
7399 AAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATATAAAATTG cjb111_all.seq
7401 AAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATATAAAATTG nem316_all.seq
7400 AAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATATAAAATTG a909_all.seq
AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA Majority
7460 7470 7480 7490 7500
7444 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA 2603_all.seq
7217 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA 18rs21_all.seq
7449 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA cohl_all.seq
7449 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA cjb111_all.seq
7451 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA nem316_all.seq
7450 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA a909_all.seq
CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA Majority
7510 7520 7530 7540 7550
7494 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA 2603_all.seq
7267 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA 18rs21_all.seq
7499 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA cohl_all.seq
7499 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA cjb111_all.seq
7501 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA nem316_all.seq
7500 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA a909_all.seq
AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA Majority
7560 7570 7580 7590 7600
544 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA 2603_all.seq
317 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA 18rs21_all.seq
549 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA cohl_all.seq
549 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA cjb111_all.seq
551 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA nem316_all.seq
550 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA a909_all.seq
AGCTGATTGATAAAATTACATCAAATAAAGACAATAGAGTAGCTCTTGTG Majority
7610 7620 7630 7640 7650
594 AGCTGATTGATAAAATTACATCAAATAAAGACAATAGAGTAGCTCTTGTG 2603_all.seq
367 AGCTGATTGATAAAATTACATCAAATAAAGACAATAGAGTAGCTCTTGTG 18rs21_all.seq
599 AGCTGATTGATAAAATTACATCAAATAAAGACAATAGAGTAGCTCTTGTG cohl_all.seq
599 AGCTGATTGATAAAATTACATCAAATAAAGACAATAGAGTAGCTCTTGTG cjb111_all.seq
601 AGCTGATTGATAAAATTACATCAAATAAAGACAATAGAGTAGCTCTTGTG nem316_all.seq
600 AGCTGATTGATAAAATTACATCAAATAAAGACAATAGAGTAGCTCTTGTG a909_all.seq
ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG Majority
7660 7670 7680 7690 7700
644 ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG 2603_all.seq
417 ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG 18rs21_all.seq
649 ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG cohl_all.seq
649 ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG cjb111_all.seq
651 ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG nem316_all.seq
650 ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG a909_all.seq

FIGURE 18 U


AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATT Majority
7710 7720 7730 7740 7750
7694 AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATT 2603_all.seq
7467 AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATT 18rs21_all.seq
7699 AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATT cohl_all.seq
7699 AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATT cjb111_all.seq
7701 AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATT nem316_all.seq
7700 AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATT a909_all.seq
ATCATAAAACTACTTTTACAGCAACTACACATAATTACAGTTATTTAAAT Majority
7760 7770 7780 7790 7800
7744 ATCATAAAACTACTTTTACAGCAACTACACATAATTACAGTTATTTAAAT 2603_all.seq
7517 ATCATAAAACTACTTTTACAGCAACTACACATAATTACAGTTATTTAAAT 18rs21_all.seq
7749 ATCATAAAACTACTTTTACAGCAACTACACATAATTACAGTTATTTAAAT cohl_all.seq
7749 ATCATAAAACTACTTTTACAGCAACTACACATAATTACAGTTATTTAAAT cjb111_all.seq
7751 ATCATAAAACTACTTTTACAGCAACTACACATAATTACAGTTATTTAAAT nem316_all.seq
7750 ATCATAAAACTACTTTTACAGCAACTACACATAATTACAGTTATTTAAAT a909_all.seq
TTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAA Majority
7810 7820 7830 7840 7850
7794 TTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAA 2603_all.seq
7567 TTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAA 18rs21_all.seq
7799 TTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAA cohl_all.seq
7799 TTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAA cjb111_all.seq
7801 TTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAA nem316_all.seq
7800 TTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAA a909_all.seq
GGAAGCGGAGCATATAAATGGGGATCGCACGCTCTATCAATTTGGTGCGA Majority
7860 7870 7880 7890 7900
7844 GGAAGCGGAGCATATAAATGGGGATCGCACGCTCTATCAATTTGGTGCGA 2603_all.seq
7617 GGAAGCGGAGCATATAAATGGGGATCGCACGCTCTATCAATTTGGTGCGA 18rs21_all.seq
7849 GGAAGCGGAGCATATAAATGGGGATCGCACGCTCTATCAATTTGGTGCGA cohl_all.seq
7849 GGAAGCGGAGCATATAAATGGGGATCGCACGCTCTATCAATTTGGTGCGA cjb111_all.seq
7851 GGAAGCGGAGCATATAAATGGGGATCGCACGCTCTATCAATTTGGTGCGA nem316_all.seq
7850 GGAAGCGGAGCATATAAATGGGGATCGCACGCTCTATCAATTTGGTGCGA a909_all.seq
CATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAA Majority
7910 7920 7930 7940 7950
7894 CATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAA 2603_all.seq
7667 CATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAA 18rs21_all.seq
7899 CATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAA cohl_all.seq
7899 CATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAA cjb111_all.seq
7901 CATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAA nem316_all.seq
7900 CATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAA a909_all.seq
AGTTCTAATGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCC Majority
7960 7970 7980 7990 8000
7944 AGTTCTAATGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCC 2603_all.seq
7717 AGTTCTAATGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCC 18rs21_all.seq
7949 AGTTCTAATGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCC cohl_all.seq
7949 AGTTCTAATGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCC cjb111_all.seq
7951 AGTTCTAATGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCC nem316_all.seq
7950 AGTTCTAATGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCC a909_all.seq
TACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACATCTTACC Majority
8010 8020 8030 8040 8050
7994 TACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACATCTTACC 2603_all.seq
7767 TACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACATCTTACC 18rs21_all.seq
7999 TACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACATCTTACC cohl_all.seq
7999 TACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACATCTTACC cjb111_all.seq
8001 TACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACATCTTACC nem316_all.seq
8000 TACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACATCTTACC a909_all.seq

FIGURE 18 V

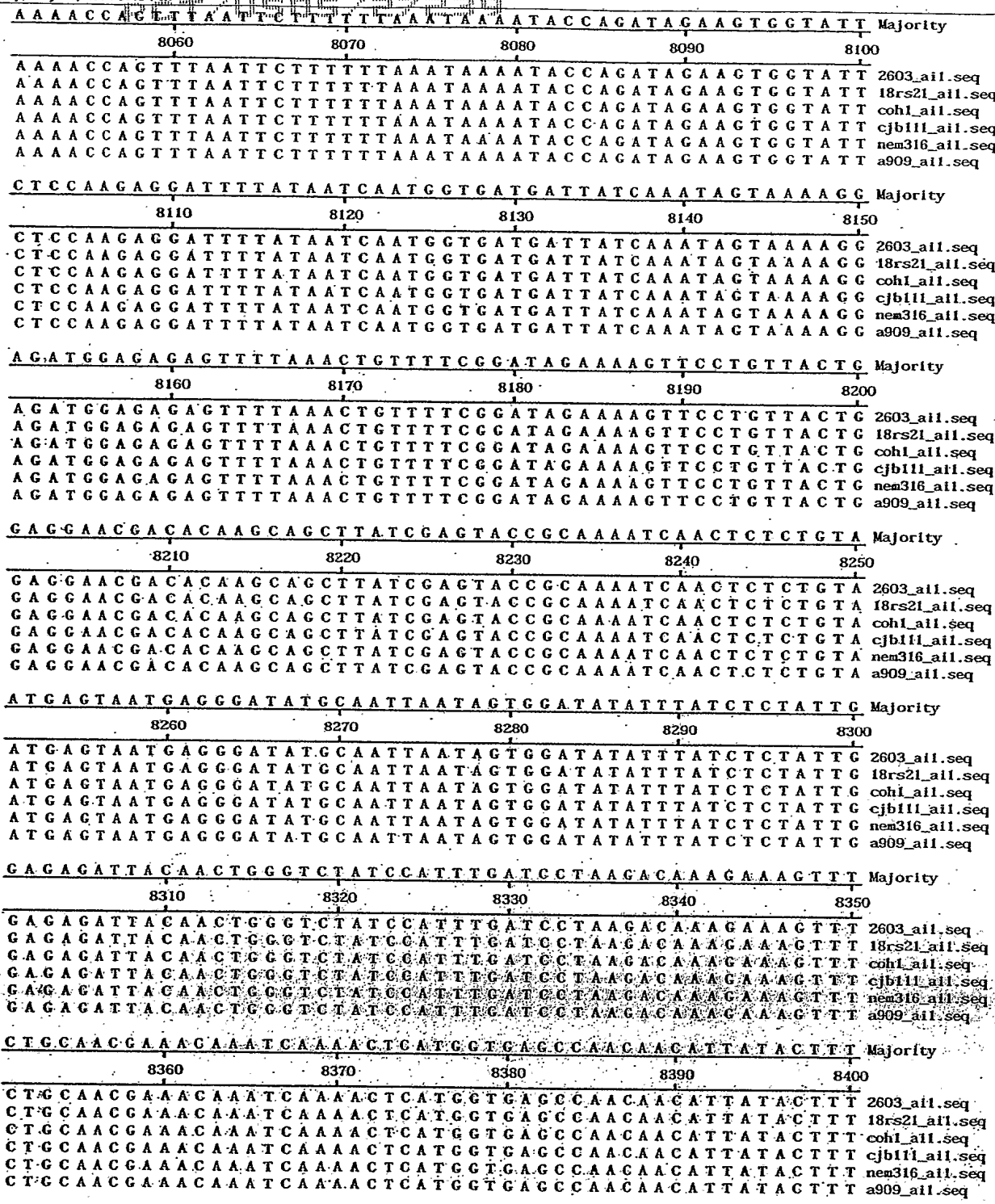
AAAACCAGTTAATTCTTTTTAAATAAAATACCAGATAGAAGTGGTATT Majority
8060 8070 8080 8090 8100
8044 AAAACCAGTTTAATTCTTTTTTAAATAAAATACCAGATAGAAGTGGTATT 2603_all.seq
7817 AAAACCAGTTTAATTCTTTTTTAAATAAAATACCAGATAGAAGTGGTATT 18rs21_all.seq
8049 AAAACCAGTTTAATTCTTTTTTAAATAAAATACCAGATAGAAGTGGTATT coh1_all.seq
8049 AAAACCAGTTTAATTCTTTTTTAAATAAAATACCAGATAGAAGTGGTATT cjb111_all.seq
8051 AAAACCAGTTTAATTCTTTTTTAAATAAAATACCAGATAGAAGTGGTATT nem316_all.seq
8050 AAAACCAGTTTAATTCTTTTTTAAATAAAATACCAGATAGAAGTGGTATT a909_all.seq
CTCCAAGAGGATTTTATAATCAATGGTGATGATTATCAAATAGTAAAAGG Majority
8110 8120 8130 8140 8150
8094 CTCCAAGAGGATTTTATAATCAATGGTGATGATTATCAAATAGTAAAAGG 2603_all.seq
7867 CTCCAAGAGGATTTTATAATCAATGGTGATGATTATCAAATAGTAAAAGG 18rs21_all.seq
8099 CTCCAAGAGGATTTTATAATCAATGGTGATGATTATCAAATAGTAAAAGG coh1_all.seq
8099 CTCCAAGAGGATTTTATAATCAATGGTGATGATTATCAAATAGTAAAAGG cjb111_all.seq
8101 CTCCAAGAGGATTTTATAATCAATGGTGATGATTATCAAATAGTAAAAGG nem316_all.seq
8100 CTCCAAGAGGATTTTATAATCAATGGTGATGATTATCAAATAGTAAAAGG a909_all.seq
AGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTG Majority
8160 8170 8180 8190 8200
8144 AGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTG 2603_all.seq
7917 AGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTG 18rs21_all.seq
8149 AGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTG coh1_all.seq
8149 AGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTG cjb111_all.seq
8151 AGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTG nem316_all.seq
8150 AGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTG a909_all.seq
GAGGAACGACACAAGCAGCTTATCGAGTACCGCAAAATCAACTCTCTGTA Majority
8210 8220 8230 8240 8250
8194 GAGGAACGACACAAGCAGCTTATCGAGTACCGCAAAATCAACTCTCTGTA 2603_all.seq
7967 GAGGAACGACACAAGCAGCTTATCGAGTACCGCAAAATCAACTCTCTGTA 18rs21_all.seq
8199 GAGGAACGACACAAGCAGCTTATCGAGTACCGCAAAATCAACTCTCTGTA coh1_all.seq
8199 GAGGAACGACACAAGCAGCTTATCGAGTACCGCAAAATCAACTCTCTGTA cjb111_all.seq
8201 GAGGAACGACACAAGCAGCTTATCGAGTACCGCAAAATCAACTCTCTGTA nem316_all.seq
8200 GAGGAACGACACAAGCAGCTTATCGAGTACCGCAAAATCAACTCTCTGTA a909_all.seq
ATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTG Majority
8260 8270 8280 8290 8300
8244 ATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTG 2603_all.seq
8017 ATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTG 18rs21_all.seq
8249 ATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTG coh1_all.seq
8249 ATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTG cjb111_all.seq
8251 ATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTG nem316_all.seq
8250 ATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTG a909_all.seq
GAGAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTT Majority
8310 8320 8330 8340 8350
8294 GAGAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTT 2603_all.seq
8067 GAGAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTT 18rs21_all.seq
8299 GAGAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTT coh1_all.seq
8299 GAGAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTT cjb111_all.seq
8301 GAGAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTT nem316_all.seq
8300 GAGAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTT a909_all.seq
CTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACAACATTATACTTT Majority
8360 8370 8380 8390 8400
8344 CTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACAACATTATACTTT 2603_all.seq
8117 CTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACAACATTATACTTT 18rs21_all.seq
8349 CTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACAACATTATACTTT coh1_all.seq
8349 CTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACAACATTATACTTT cjb111_all.seq
8351 CTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACAACATTATACTTT nem316_all.seq
8350 CTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACAACATTATACTTT a909_all.seq

FIGURE 18 W

	AATGCAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGCATTGG	Majority
	8410 8420 8430 8440 8450	
8394	AATGCAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGCATTGG	2603_ai1.seq
8167	AATGCAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGCATTGG	18rs21_ai1.seq
8399	AATGCAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGCATTGG	coh1_ai1.seq
8399	AATGCAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGCATTGG	cjb111_ai1.seq
8401	AATGCAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGCATTGG	nem316_ai1.seq
8400	AATGCAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGCATTGG	a909_ai1.seq
	TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC	Majority
	8460 8470 8480 8490 8500	
8444	TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC	2603_ai1.seq
8217	TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC	18rs21_ai1.seq
8449	TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC	coh1_ai1.seq
8449	TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC	cjb111_ai1.seq
8451	TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC	nem316_ai1.seq
8450	TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC	a909_ai1.seq
	AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT	Majority
	8510 8520 8530 8540 8550	
8494	AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT	2603_ai1.seq
8267	AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT	18rs21_ai1.seq
8499	AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT	coh1_ai1.seq
8499	AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT	cjb111_ai1.seq
8501	AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT	nem316_ai1.seq
8500	AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT	a909_ai1.seq
	AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA	Majority
	8560 8570 8580 8590 8600	
8544	AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA	2603_ai1.seq
8317	AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA	18rs21_ai1.seq
8549	AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA	coh1_ai1.seq
8549	AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA	cjb111_ai1.seq
8551	AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA	nem316_ai1.seq
8550	AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA	a909_ai1.seq
	ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG	Majority
	8610 8620 8630 8640 8650	
8594	ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG	2603_ai1.seq
8367	ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG	18rs21_ai1.seq
8599	ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG	coh1_ai1.seq
8599	ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG	cjb111_ai1.seq
8601	ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG	nem316_ai1.seq
8600	ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG	a909_ai1.seq
	AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTG	Majority
	8660 8670 8680 8690 8700	
8644	AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTG	2603_ai1.seq
8417	AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTG	18rs21_ai1.seq
8649	AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTG	coh1_ai1.seq
8649	AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTG	cjb111_ai1.seq
8651	AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTG	nem316_ai1.seq
8650	AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTG	a909_ai1.seq
	GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGTGGCTCTTGGTGGACC	Majority
	8710 8720 8730 8740 8750	
8694	GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGTGGCTCTTGGTGGACC	2603_ai1.seq
8467	GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGTGGCTCTTGGTGGACC	18rs21_ai1.seq
8699	GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGTGGCTCTTGGTGGACC	coh1_ai1.seq
8699	GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGTGGCTCTTGGTGGACC	cjb111_ai1.seq
8701	GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGTGGCTCTTGGTGGACC	nem316_ai1.seq
8700	GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGTGGCTCTTGGTGGACC	a909_ai1.seq

FIGURE 18 X

```
     AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA Majority
               8760      8770      8780      8790      8800
8744 AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA 2603_all.seq
8517 AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA 18rs21_all.seq
8749 AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA coh1_all.seq
8749 AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA cjb111_all.seq
8751 AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA nem316_all.seq
8750 AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA a909_all.seq

     CATCTCAAACCATCAAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA Majority
               8810      8820      8830      8840      8850
8794 CATCTCAAACCATCAAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA 2603_all.seq
8567 CATCTCAAACCATCAAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA 18rs21_all.seq
8799 CATCTCAAACCATCAAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA coh1_all.seq
8799 CATCTCAAACCATCAAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA cjb111_all.seq
8801 CATCTCAAACCATCAAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA nem316_all.seq
8800 CATCTCAAACCATCAAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA a909_all.seq

     GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA Majority
               8860      8870      8880      8890      8900
8844 GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA 2603_all.seq
8617 GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA 18rs21_all.seq
8849 GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA coh1_all.seq
8849 GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA cjb111_all.seq
8851 GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA nem316_all.seq
8850 GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA a909_all.seq

     ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG Majority
               8910      8920      8930      8940      8950
8894 ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG 2603_all.seq
8667 ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG 18rs21_all.seq
8899 ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG coh1_all.seq
8899 ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG cjb111_all.seq
8901 ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG nem316_all.seq
8900 ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG a909_all.seq

     AACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCGTGATGTTCGT Majority
               8960      8970      8980      8990      9000
8944 AACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCGTGATGTTCGT 2603_all.seq
8717 AACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCGTGATGTTCGT 18rs21_all.seq
8949 AACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCGTGATGTTCGT coh1_all.seq
8949 AACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCGTGATGTTCGT cjb111_all.seq
8951 AACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCGTGATGTTCGT nem316_all.seq
8950 AACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCGTGATGTTCGT a909_all.seq

     GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGA Majority
               9010      9020      9030      9040      9050
8994 GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGA 2603_all.seq
8767 GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGA 18rs21_all.seq
8999 GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGA coh1_all.seq
8999 GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGA cjb111_all.seq
9001 GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGA nem316_all.seq
9000 GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGA a909_all.seq

     ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA Majority
               9060      9070      9080      9090      9100
9044 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA 2603_all.seq
8817 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA 18rs21_all.seq
9049 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA coh1_all.seq
9049 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA cjb111_all.seq
9051 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA nem316_all.seq
9050 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA a909_all.seq
```

FIGURE 18 Y

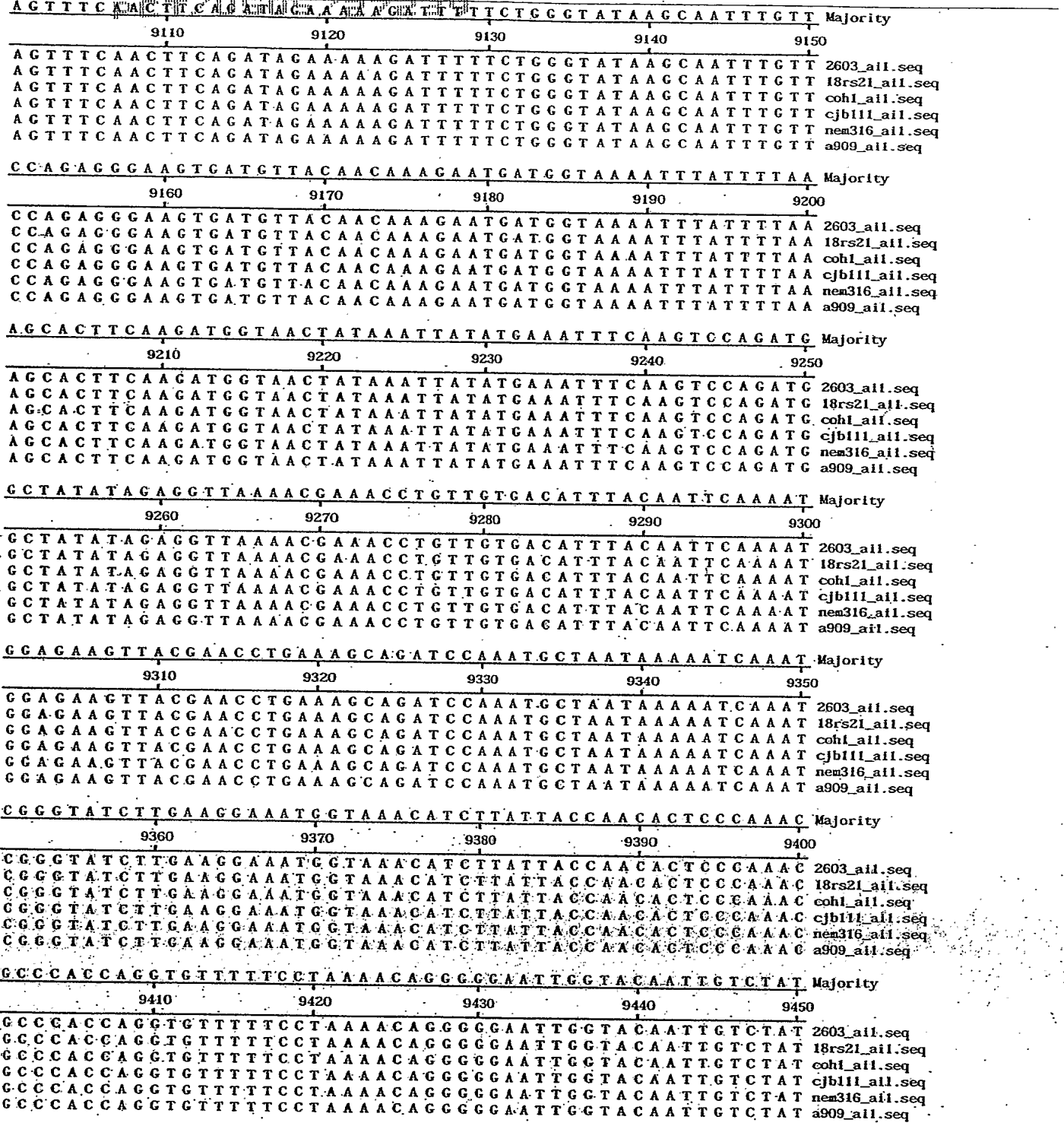
Majority
9110 9120 9130 9140 9150
9094 AGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTT 2603_all.seq
8867 AGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTT 18rs21_all.seq
9099 AGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTT cohl_all.seq
9099 AGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTT cjb111_all.seq
9101 AGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTT nem316_all.seq
9100 AGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTT a909_all.seq
Majority
9160 9170 9180 9190 9200
9144 CCAGAGGGAAGTGATGTTACAACAAAGAATGATGGTAAAATTTATTTTAA 2603_all.seq
8917 CCAGAGGGAAGTGATGTTACAACAAAGAATGATGGTAAAATTTATTTTAA 18rs21_all.seq
9149 CCAGAGGGAAGTGATGTTACAACAAAGAATGATGGTAAAATTTATTTTAA cohl_all.seq
9149 CCAGAGGGAAGTGATGTTACAACAAAGAATGATGGTAAAATTTATTTTAA cjb111_all.seq
9151 CCAGAGGGAAGTGATGTTACAACAAAGAATGATGGTAAAATTTATTTTAA nem316_all.seq
9150 CCAGAGGGAAGTGATGTTACAACAAAGAATGATGGTAAAATTTATTTTAA a909_all.seq
Majority
9210 9220 9230 9240 9250
9194 AGCACTTCAAGATGGTAACTATAAATTATATGAAATTTCAAGTCCAGATG 2603_all.seq
8967 AGCACTTCAAGATGGTAACTATAAATTATATGAAATTTCAAGTCCAGATG 18rs21_all.seq
9199 AGCACTTCAAGATGGTAACTATAAATTATATGAAATTTCAAGTCCAGATG cohl_all.seq
9199 AGCACTTCAAGATGGTAACTATAAATTATATGAAATTTCAAGTCCAGATG cjb111_all.seq
9201 AGCACTTCAAGATGGTAACTATAAATTATATGAAATTTCAAGTCCAGATG nem316_all.seq
9200 AGCACTTCAAGATGGTAACTATAAATTATATGAAATTTCAAGTCCAGATG a909_all.seq
Majority
9260 9270 9280 9290 9300
9244 GCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAAT 2603_all.seq
9017 GCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAAT 18rs21_all.seq
9249 GCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAAT cohl_all.seq
9249 GCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAAT cjb111_all.seq
9251 GCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAAT nem316_all.seq
9250 GCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAAT a909_all.seq
Majority
9310 9320 9330 9340 9350
9294 GGAGAAGTTACGAACCTGAAAGCAGATCCAAATGCTAATAAAAATCAAAT 2603_all.seq
9067 GGAGAAGTTACGAACCTGAAAGCAGATCCAAATGCTAATAAAAATCAAAT 18rs21_all.seq
9299 GGAGAAGTTACGAACCTGAAAGCAGATCCAAATGCTAATAAAAATCAAAT cohl_all.seq
9299 GGAGAAGTTACGAACCTGAAAGCAGATCCAAATGCTAATAAAAATCAAAT cjb111_all.seq
9301 GGAGAAGTTACGAACCTGAAAGCAGATCCAAATGCTAATAAAAATCAAAT nem316_all.seq
9300 GGAGAAGTTACGAACCTGAAAGCAGATCCAAATGCTAATAAAAATCAAAT a909_all.seq
Majority
9360 9370 9380 9390 9400
9344 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC 2603_all.seq
9117 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC 18rs21_all.seq
9349 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC cohl_all.seq
9349 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC cjb111_all.seq
9351 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC nem316_all.seq
9350 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC a909_all.seq
Majority
9410 9420 9430 9440 9450
9394 GCCCACCAGGTGTTTTTCCTAAAACAGGGGCGAATTGGTACAATTGTCTAT 2603_all.seq
9167 GCCCACCAGGTGTTTTTCCTAAAACAGGGGCGAATTGGTACAATTGTCTAT 18rs21_all.seq
9399 GCCCACCAGGTGTTTTTCCTAAAACAGGGGCGAATTGGTACAATTGTCTAT cohl_all.seq
9399 GCCCACCAGGTGTTTTTCCTAAAACAGGGGCGAATTGGTACAATTGTCTAT cjb111_all.seq
9401 GCCCACCAGGTGTTTTTCCTAAAACAGGGGCGAATTGGTACAATTGTCTAT nem316_all.seq
9400 GCCCACCAGGTGTTTTTCCTAAAACAGGGGCGAATTGGTACAATTGTCTAT a909_all.seq

FIGURE 18 Z

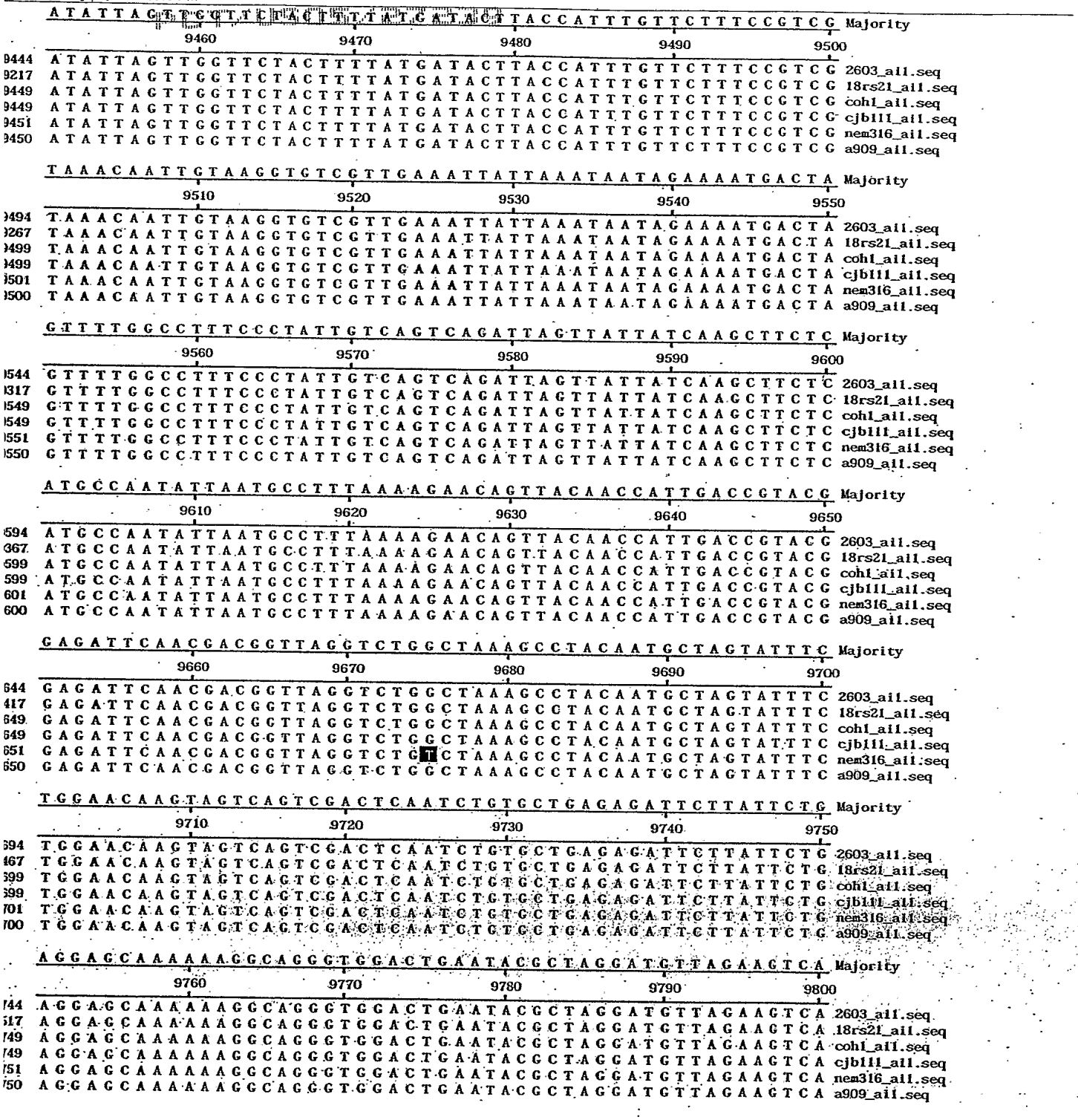
Majority
2603_all.seq
18rs21_all.seq
cohl_all.seq
cjblll_all.seq
nem316_all.seq
a909_all.seq

FIGURE 18 AA

```
      GAGAGCAGGTTGACCATGTGATGATTCCAAAAATCAATCAGGATTTACCA Majority
               9810      9820      9830      9840      9850
9794  GAGAGCAGGTTGACCATGTGATGATTCCAAAAATCAATCAGGATTTACCA 2603_ai1.seq
9567  GAGAGCAGGTTGACCATGTGATGATTCCAAAAATCAATCAGGATTTACCA 18rs21_ai1.seq
9799  GAGAGCAGGTTGACCATGTGATGATTCCAAAAATCAATCAGGATTTACCA coh1_ai1.seq
9799  GAGAGCAGGTTGACCATGTGATGATTCCAAAAATCAATCAGGATTTACCA cjb111_ai1.seq
9801  GAGAGCAGGTTGACCATGTGATGATTCCAAAAATCAATCAGGATTTACCA nem316_ai1.seq
9800  GAGAGCAGGTTGACCATGTGATGATTCCAAAAATCAATCAGGATTTACCA a909_ai1.seq

      ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT Majority
               9860      9870      9880      9890      9900
9844  ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT 2603_ai1.seq
9617  ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT 18rs21_ai1.seq
9849  ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT coh1_ai1.seq
9849  ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT cjb111_ai1.seq
9851  ATCTACGCTGGTCCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT nem316_ai1.seq
9850  ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT a909_ai1.seq

      AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA Majority
               9910      9920      9930      9940      9950
9894  AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA 2603_ai1.seq
9667  AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA 18rs21_ai1.seq
9899  AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA coh1_ai1.seq
9899  AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA cjb111_ai1.seq
9901  AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA nem316_ai1.seq
9900  AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA a909_ai1.seq

      GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG Majority
               9960      9970      9980      9990      10000
9944  GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG 2603_ai1.seq
9717  GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG 18rs21_ai1.seq
9949  GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG coh1_ai1.seq
9949  GCGGTCAAAGAGGTATGTCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG cjb111_ai1.seq
9951  GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG nem316_ai1.seq
9950  GCGGTCAAAGAGGTATGTCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG a909_ai1.seq

      ATGAAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAAACCTTGGC Majority
               10010     10020     10030     10040     10050
994   ATGAAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAAACCTTGGC 2603_ai1.seq
767   ATGAAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAAACCTTGGC 18rs21_ai1.seq
999   ATGAAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAAACCTTGGC coh1_ai1.seq
999   ATGAAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAAACCTTGGC cjb111_ai1.seq
0001  ATGAAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAAACCTTGGC nem316_ai1.seq
0000  ATGAAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAAACCTTGGC a909_ai1.seq

      TTATCAAGTGGATCGTATCATGGTGATTGAACCTAGCCAATTGGATGCCG Majority
               10060     10070     10080     10090     10100
0044  TTATCAAGTGGATCGTATCATGGTGATTGAACCTAGCCAATTGGATGCCG 2603_ai1.seq
817   TTATCAAGTGGATCGTATCATGGTGATTGAACCTAGCCAATTGGATGCCG 18rs21_ai1.seq
0049  TTATCAAGTGGATCGTATCATGGTGATTGAACCTAGCCAATTGGATGCCG coh1_ai1.seq
0049  TTATCAAGTGGATCGTATCATGGTGATTGAACCTAGCCAATTGGATGCCG cjb111_ai1.seq
0051  TTATCAAGTGGATCGTATCATGGTGATTGAACCTAGCCAATTGGATGCCG nem316_ai1.seq
0050  TTATCAAGTGGATCGTATCATGGTGATTGAACCTAGCCAATTGGATGCCG a909_ai1.seq

      TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT Majority
               10110     10120     10130     10140     10150
0094  TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT 2603_ai1.seq
867   TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT 18rs21_ai1.seq
0099  TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT coh1_ai1.seq
0099  TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT cjb111_ai1.seq
0101  TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT nem316_ai1.seq
0100  TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT a909_ai1.seq
```

FIGURE 18 AB

```
      TATATGGGCTCTTTGTCAACTGTAATGGGTGACTTATCATTAACAACGAG Majority
            10160     10170     10180     10190     10200
10144 TATATGGGCTCTTTGTCAACTGTAATGGGTGACTTATCATTAACAACGAG 2603_all.seq
9917  TATATGGGCTCTTTGTCAACTGTAATGGGTGACTTATCATTAACAACGAG 18rs21_all.seq
10149 TATATGGGCTCTTTGTCAACTGTAATGGGTGACTTATCATTAACAACGAG coh1_all.seq
10149 TATATGGGCTCTTTGTCAACTGTAATGGGTGACTTATCATTAACAACGAG cjb111_all.seq
10151 TATATGGGCTCTTTGTCAACTGTAATGGGTGACTTATCATTAACAACGAG nem316_all.seq
10150 TATATGGGCTCTTTGTCAACTGTAATGGGTGACTTATCATTAACAACGAG a909_all.seq

      AGAGAATCAGCTTGGTTCTCTCTCTTTTTGGATGTTCAAAGCGATGAGAA Majority
            10210     10220     10230     10240     10250
10194 AGAGAATCAGCTTGGTTCTCTCTCTTTTTGGATGTTCAAAGCGATGAGAA 2603_all.seq
9967  AGAGAATCAGCTTGGTTCTCTCTCTTTTTGGATGTTCAAAGCGATGAGAA 18rs21_all.seq
10199 AGAGAATCAGCTTGGTTCTCTCTCTTTTTGGATGTTCAAAGCGATGAGAA coh1_all.seq
10199 AGAGAATCAGCTTGGTTCTCTCTCTTTTTGGATGTTCAAAGCGATGAGAA cjb111_all.seq
10201 AGAGAATCAGCTTGGTTCTCTCTCTTTTTGGATGTTCAAAGCGATGAGAA nem316_all.seq
10200 AGAGAATCAGCTTGGTTCTCTCTCTTTTTGGATGTTCAAAGCGATGAGAA a909_all.seq

      TTTTGCTTTTAAAATTTTTAAAGTTGCGAAAGCCAAAGGCTTGTCGCTTG Majority
            10260     10270     10280     10290     10300
10244 TTTTGCTTTTAAAATTTTTAAAGTTGCGAAAGCCAAAGGCTTGTCGCTTG 2603_all.seq
10017 TTTTGCTTTTAAAATTTTTAAAGTTGCGAAAGCCAAAGGCTTGTCGCTTG 18rs21_all.seq
10249 TTTTGCTTTTAAAATTTTTAAAGTTGCGAAAGCCAAAGGCTTGTCGCTTG coh1_all.seq
10249 TTTTGCTTTTAAAATTTTTAAAGTTGCGAAAGCCAAAGGCTTGTCGCTTG cjb111_all.seq
10251 TTTTGCTTTTAAAATTTTTAAAGTTGCGAAAGCCAAAGGCTTGTCGCTTG nem316_all.seq
10250 TTTTGCTTTTAAAATTTTTAAAGTTGCGAAAGCCAAAGGCTTGTCGCTTG a909_all.seq

      ATGTCTTTGATAAGCTTGTTGGTCGCTTCTAATTTGGCATTGGAAAGGGA Majority
            10310     10320     10330     10340     10350
10294 ATGTCTTTGATAAGCTTGTTGGTCGCTTCTAATTTGGCATTGGAAAGGGA 2603_all.seq
10067 ATGTCTTTGATAAGCTTGTTGGTCGCTTCTAATTTGGCATTGGAAAGGGA 18rs21_all.seq
10299 ATGTCTTTGATAAGCTTGTTGGTCGCTTCTAATTTGGCATTGGAAAGGGA coh1_all.seq
10299 ATGTCTTTGATAAGCTTGTTGGTCGCTTCTAATTTGGCATTGGAAAGGGA cjb111_all.seq
10301 ATGTCTTTGATAAGCTTGTTGGTCGCTTCTAATTTGGCATTGGAAAGGGA nem316_all.seq
10300 ATGTCTTTGATAAGCTTGTTGGTCGCTTCTAATTTGGCATTGGAAAGGGA a909_all.seq

      TAGCTGAGGGCGTTTGTGATGTAAGTTTTGTACTTCATGAAGGTCCTAAA Majority
            10360     10370     10380     10390     10400
10344 TAGCTGAGGGCGTTTGTGATGTAAGTTTTGTACTTCATGAAGGTCCTAAA 2603_all.seq
10117 TAGCTGAGGGCGTTTGTGATGTAAGTTTTGTACTTCATGAAGGTCCTAAA 18rs21_all.seq
10349 TAGCTGAGGGCGTTTGTGATGTAAGTTTTGTACTTCATGAAGGTCCTAAA coh1_all.seq
10349 TAGCTGAGGGCGTTTGTGATGTAAGTTTTGTACTTCATGAAGGTCCTAAA cjb111_all.seq
0351  TAGCTGAGGGCGTTTGTGATGTAAGTTTTGTACTTCATGAAGGTCCTAAA nem316_all.seq
0350  TAGCTGAGGGCGTTTGTGATGTAAGTTTTGTACTTCATGAAGGTCCTAAA a909_all.seq

      GACCATTTTAAAAGCAGAATTGCCAGTTGTTACGTTATCATCTATGAAGC Majority
            10410     10420     10430     10440     10450
0394  GACCATTTTAAAAGCAGAATTGCCAGTTGTTACGTTATCATCTATGAAGC 2603_all.seq
0167  GACCATTTTAAAAGCAGAATTGCCAGTTGTTACGTTATCATCTATGAAGC 18rs21_all.seq
0399  GACCATTTTAAAAGCAGAATTGCCAGTTGTTACGTTATCATCTATGAAGC coh1_all.seq
0399  GACCATTTTAAAAGCAGAATTGCCAGTTGTTACGTTATCATCTATGAAGC cjb111_all.seq
0401  GACCATTTTAAAAGCAGAATTGCCAGTTGTTACGTTATCATCTATGAAGC nem316_all.seq
0400  GACCATTTTAAAAGCAGAATTGCCAGTTGTTACGTTATCATCTATGAAGC a909_all.seq

      TAAAGAATTCAGTTGTTCGCTTTTCTTAGAAATGAAAGAGTATGAGCTGA Majority
            10460     10470     10480     10490     10500
0444  TAAAGAATTCAGTTGTTCGCTTTTCTTAGAAATGAAAGAGTATGAGCTGA 2603_all.seq
0217  TAAAGAATTCAGTTGTTCGCTTTTCTTAGAAATGAAAGAGTATGAGCTGA 18rs21_all.seq
0449  TAAAGAATTCAGTTGTTCGCTTTTCTTAGAAATGAAAGAGTATGAGCTGA coh1_all.seq
0449  TAAAGAATTCAGTTGTTCGCTTTTCTTAGAAATGAAAGAGTATGAGCTGA cjb111_all.seq
0451  TAAAGAATTCAGTTGTTCGCTTTTCTTAGAAATGAAAGAGTATGAGCTGA nem316_all.seq
0450  TAAAGAATTCAGTTGTTCGCTTTTCTTAGAAATGAAAGAGTATGAGCTGA a909_all.seq
```

FIGURE 18 AC

```
      TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA Majority
                10510       10520       10530       10540       10550
10494 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA 2603_all.seq
10267 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA 18rs21_all.seq
10499 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA cohl_all.seq
10499 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA cjb111_all.seq
10501 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA nem316_all.seq
10500 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA a909_all.seq

      AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC Majority
                10560       10570       10580       10590       10600
10544 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC 2603_all.seq
10317 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC 18rs21_all.seq
10549 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC cohl_all.seq
10549 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC cjb111_all.seq
10551 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC nem316_all.seq
10550 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC a909_all.seq

      TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA Majority
                10610       10620       10630       10640       10650
10594 TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA 2603_all.seq
10367 TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA 18rs21_all.seq
10599 TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA cohl_all.seq
10599 TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA cjb111_all.seq
10601 TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA nem316_all.seq
10600 TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA a909_all.seq

      AAAGTTCTATCATCCTCTTTTGGCGCCTTTTTTCCAGCAGATAATATTAA Majority
                10660       10670       10680       10690       10700
10644 AAAGTTCTATCATCCTCTTTTGGCGCCTTTTTTCCAGCAGATAATATTAA 2603_all.seq
10417 AAAGTTCTATCATCCTCTTTTGGCGCCTTTTTTCCAGCAGATAATATTAA 18rs21_all.seq
10649 AAAGTTCTATCATCCTCTTTTGGCGCCTTTTTTCCAGCAGATAATATTAA cohl_all.seq
10649 AAAGTTCTATCATCCTCTTTTGGCGCCTTTTTTCCAGCAGATAATATTAA cjb111_all.seq
10651 AAAGTTCTATCATCCTCTTTTGGCGCCTTTTTTCCAGCAGATAATATTAA nem316_all.seq
10650 AAAGTTCTATCATCCTCTTTTGGCGCCTTTTTTCCAGCAGATAATATTAA a909_all.seq

      GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG Majority
                10710       10720       10730       10740       10750
0694 GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG 2603_all.seq
0467 GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG 18rs21_all.seq
0699 GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG cohl_all.seq
0699 GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG cjb111_all.seq
0701 GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG nem316_all.seq
0700 GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG a909_all.seq

      CAAACTACACCACTCAGATTCAAGCTATTGGGACAACGATTAAGTCACAA Majority
                10760       10770       10780       10790       10800
0744 CAAACTACACCACTCAGATTCAAGCTATTGGGACAACGATTAAGTCACAA 2603_all.seq
0517 CAAACTACACCACTCAGATTCAAGCTATTGGGACAACGATTAAGTCACAA 18rs21_all.seq
0749 CAAACTACACCACTCAGATTCAAGCTATTGGGACAACGATTAAGTCACAA cohl_all.seq
0749 CAAACTACACCACTCAGATTCAAGCTATTGGGACAACGATTAAGTCACAA cjb111_all.seq
0751 CAAACTACACCACTCAGATTCAAGCTATTGGGACAACGATTAAGTCACAA nem316_all.seq
0750 CAAACTACACCACTCAGATTCAAGCTATTGGGACAACGATTAAGTCACAA a909_all.seq

      ATTCCGGAATCGATTTTGACGGTTACGGATAAAAAGAGCAGGAAGTTCAG Majority
                10810       10820       10830       10840       10850
0794 ATTCCGGAATCGATTTTGACGGTTACGGATAAAAAGAGCAGGAAGTTCAG 2603_all.seq
0567 ATTCCGGAATCGATTTTGACGGTTACGGATAAAAAGAGCAGGAAGTTCAG 18rs21_all.seq
0799 ATTCCGGAATCGATTTTGACGGTTACGGATAAAAAGAGCAGGAAGTTCAG cohl_all.seq
0799 ATTCCGGAATCGATTTTGACGGTTACGGATAAAAAGAGCAGGAAGTTCAG cjb111_all.seq
0801 ATTCCGGAATCGATTTTGACGATTACGGATAAAAAGAGCAGGAAGTTCAG nem316_all.seq
0800 ATTCCGGAATCGATTTTGACGGTTACGGATAAAAAGAGCAGGAAGTTCAG a909_all.seq
```

FIGURE 18 AD

```
                CATTAACAACATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA Majority
                        10860     10870     10880     10890     10900
10844 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA
10617 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA 2603_all.seq
10849 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA 18rs21_all.seq
10849 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA cohl_all.seq
10851 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA cjb111_all.seq
10850 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA nem316_all.seq
                CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA a909_all.seq

                CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT Majority
                        10910     10920     10930     10940     10950
10894 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT
10667 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT 2603_all.seq
10899 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT 18rs21_all.seq
10899 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT cohl_all.seq
10901 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT cjb111_all.seq
10900 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT nem316_all.seq
                CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT a909_all.seq

                TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT Majority
                        10960     10970     10980     10990     11000
10944 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT
10717 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT 2603_all.seq
10949 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT 18rs21_all.seq
10949 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT cohl_all.seq
10951 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACTCTTACCTT cjb111_all.seq
10950 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT nem316_all.seq
                TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACTCTTACCTT a909_all.seq

                TGACAACCTTAAACCTGGATTTTATGACCTTAAAGAAACGAAAGCGCCGA Majority
                        11010     11020     11030     11040     11050
10994 TGACAACCTTAAACCTGGATTTTATGACCTTAAAGAAACGAAAGCGCCGA
10767 TGACAACCTTAAACCTGGATTTTATGACCTTAAAGAAACGAAAGCGCCGA 2603_all.seq
10999 TGACAACCTTAAACCTGGATTTTATGACCTTAAAGAAACGAAAGCGCCGA 18rs21_all.seq
10999 TGACAACCTTAAACCTGGATTTTATGACCTTAAAGAAACGAAAGCGCCGA cohl_all.seq
11001 TGACAACCTTAAACCTGGATTTTATGACCTTAAAGAAACGAAAGCGCCGA cjb111_all.seq
11000 TGACAACCTTAAACCTGGATTTTATGACCTTAAAGAAACGAAAGCGCCGA nem316_all.seq
                TGACAACCTTAAACCTGGATTTTATGACCTTAAAGAAACGAAAGCGCCGA a909_all.seq

                ATGCTTACGTACTTGATCCTAAGACTTATGTTGTGGTCGTTCAAAATTCA Majority
                        11060     11070     11080     11090     11100
11044 ATGCTTACGTACTTGATCCTAAGACTTATGTTGTGGTCGTTCAAAATTCA
10817 ATGCTTACGTACTTGATCCTAAGACTTATGTTGTGGTCGTTCAAAATTCA 2603_all.seq
11049 ATGCTTACGTACTTGATCCTAAGACTTATGTTGTGGTCGTTCAAAATTCA 18rs21_all.seq
11049 ATGCTTACGTACTTGATCCTAAGACTTATGTTGTGGTCGTTCAAAATTCA cohl_all.seq
11051 ATGCTTACGTACTTGATCCTAAGACTTATGTTGTGGTCGTTCAAAATTCA cjb111_all.seq
11050 ATGCTTACGTACTTGATCCTAAGACTTATGTTGTGGTCGTTCAAAATTCA nem316_all.seq
                ATGCTTACGTACTTGATCCTAAGACTTATGTTGTGGTCGTTCAAAATTCA a909_all.seq

                GGAAAAACGACAATTGTGGATGAAGCTAACTTCAAAGAGGCTGATTACCC Majority
                        11110     11120     11130     11140     11150
11094 GGAAAAACGACAATTGTGGATGAAGCTAACTTCAAAGAGGCTGATTACCC
10867 GGAAAAACGACAATTGTGGATGAAGCTAACTTCAAAGAGGCTGATTACCC 2603_all.seq
11099 GGAAAAACGACAATTGTGGATGAAGCTAACTTCAAAGAGGCTGATTACCC 18rs21_all.seq
11099 GGAAAAACGACAATTGTGGATGAAGCTAACTTCAAAGAGGCTGATTACCC cohl_all.seq
11101 GGAAAAACGACAATTGTGGATGAAGCTAACTTCAAAGAGGCTGATTACCC cjb111_all.seq
11100 GGAAAAACGACAATTGTGGATGAAGCTAACTTCAAAGAGGCTGATTACCC nem316_all.seq
                GGAAAAACGACAATTGTGGATGAAGCTAACTTCAAAGAGGCTGATTACCC a909_all.seq

                AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA Majority
                        11160     11170     11180     11190     11200
11144 AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA
10917 AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA 2603_all.seq
11149 AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA 18rs21_all.seq
11149 AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA cohl_all.seq
11151 AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA cjb111_all.seq
11150 AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA nem316_all.seq
                AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA a909_all.seq
```

FIGURE 18 AE

```
      GCAAAGGGTAAAAATCCTTTATTTTAAGCACTTTTTCAAGCATTTTGTCT Majority
                11210     11220     11230     11240     11250
11194 GCAAAGGGTAAAAATCCTTTATTTTAAGCACTTTTTCAAGCATTTTGTCT 2603_ai1.seq
10967 GCAAAGGGTAAAAATCCTTTATTTTAAGCACTTTTTCAAGCATTTTGTCT 18rs21_ai1.seq
11199 GCAAAGGGTAAAAATCCTTTATTTTAAGCACTTTTTCAAGCATTTTGTCT coh1_ai1.seq
11199 GCAAAGGGTAAAAATCCTTTATTTTAAGCACTTTTTCAAGCATTTTGTCT cjb111_ai1.seq
11201 GCAAAGGGTAAAAATCCTTTATTTTAAGCACTTTTTCAAGCATTTTGTCT nem316_ai1.seq
11200 GCAAAGGGTAAAAATCCTTTATTTTAAGCACTTTTTCAAGCATTTTGTCT a909_ai1.seq

      TTATTGAAAAGAGTGATTTTAACATAAAAAAGGTATTAAAAAACATATTG Majority
                11260     11270     11280     11290     11300
11244 TTATTGAAAAGAGTGATTTTAACATAAAAAAGGTATTAAAAAACATATTG 2603_ai1.seq
11017 TTATTGAAAAGAGTGATTTTAACATAAAAAAGGTATTAAAAAACATATTG 18rs21_ai1.seq
11249 TTATTGAAAAGAGTGATTTTAACATAAAAAAGGTATTAAAAAACATATTG coh1_ai1.seq
11249 TTATTGAAAAGAGTGATTTTAACATAAAAAAGGTATTAAAAAACATATTG cjb111_ai1.seq
11251 TTATTGAAAAGAGTGATTTTAACATAAAAAAGGTATTAAAAAACATATTG nem316_ai1.seq
11250 TTATTGAAAAGAGTGATTTTAACATAAAAAAGGTATTAAAAAACATATTG a909_ai1.seq

      ACGTGACCGTTTGTTTTGAAGTGGCTTGCGTAGACAAAAAAATAGATACG Majority
                11310     11320     11330     11340     11350
11294 ACGTGACCGTTTGTTTTGAAGTGGCTTGCGTAGACAAAAAAATAGATACG 2603_ai1.seq
11067 ACGTGACCGTTTGTTTTGAAGTGGCTTGCGTAGACAAAAAAATAGATACG 18rs21_ai1.seq
11299 ACGTGACCGTTTGTTTTGAAGTGGCTTGCGTAGACAAAAAAATAGATACG coh1_ai1.seq
11299 ACGTGACCGTTTGTTTTGAAGTGGCTTGCGTAGACAAAAAAATAGATACG cjb111_ai1.seq
11301 ACGTGACCGTTTGTTTTGAAGTGGCTTGCGTAGACAAAAAAATAGATACG nem316_ai1.seq
11300 ACGTGACCGTTTGTTTTGAAGTGGCTTGCGTAGACAAAAAAATAGATACG a909_ai1.seq

      TCAGATAAATTTCTGGCATTACGAGAACATTTTTAGAGTGTTCTCTTTTT Majority
                11360     11370     11380     11390     11400
11344 TCAGATAAATTTCTGGCATTACGAGAACATTTTTAGAGTGTTCTCTTTTT 2603_ai1.seq
11117 TCAGATAAATTTCTGGCATTACGAGAACATTTTTAGAGTGTTCTCTTTTT 18rs21_ai1.seq
11349 TCAGATAAATTTCTGGCATTACGAGAACATTTTTAGAGTGTTCTCTTTTT coh1_ai1.seq
11349 TCAGATAAATTTCTGGCATTACGAGAACATTTCTAGAGTGTTCTCTTTTT cjb111_ai1.seq
11351 TCAGATAAATTTCTGGCATTACGAGAACATTTTTAGAGTGTTCTCTTTTT nem316_ai1.seq
11350 TCAGATAAATTTCTGGCATTACGAGAACATTTCTAGAGTGTTCTCTTTTT a909_ai1.seq

      TTAGTTTACGGAGGAAAAATATATATGGAAAAACAGGATTCACGAGTTCT Majority
                11410     11420     11430     11440     11450
1394  TTAGTTTACGGAGGAAAAATATATATGGAAAAACAGGATTCACGAGTTCT 2603_ai1.seq
1167  TTAGTTTACGGAGGAAAAATATATATGGAAAAACAGGATTCACGAGTTCT 18rs21_ai1.seq
1399  TTAGTTTACGGAGGAAAAATATATATGGAAAAACAGGATTCACGAGTTCT coh1_ai1.seq
1399  TTAGTTTACGGAGGAAAAATATATATGGAAAAACAGGATTCACGAGTTCT cjb111_ai1.seq
1401  TTAGTTTACGGAGGAAAAATATATATGGAAAAACAGGATTCACGAGTTCT nem316_ai1.seq
1400  TTAGTTTACGGAGGAAAAATATATATGGAAAAACAGGATTCACGAGTTCT a909_ai1.seq

      CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCAAACCA Majority
                11460     11470     11480     11490     11500
1444  CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCAAACCA 2603_ai1.seq
1217  CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCAAACCA 18rs21_ai1.seq
1449  CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCAAACCA coh1_ai1.seq
1449  CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCAAACCA cjb111_ai1.seq
1451  CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCAAACCA nem316_ai1.seq
1450  CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCAAACCA a909_ai1.seq

      GCGCAACGGGGTGGTACTACCAAGTCGATCGTAGCTTTAGTCAACCAAAA Majority
                11510     11520     11530     11540     11550
1494  GCGCAACGGGGTGGTACTACCAAGTCGATCGTAGCTTTAGTCAACCAAAA 2603_ai1.seq
1267  GCGCAACGGGGTGGTACTACCAAGTCGATCGTAGCTTTAGTCAACCAAAA 18rs21_ai1.seq
1499  GCGCAATGGGGTGGTACTACCAAGTCGATCGTAGCTTTAGTCAACCAAAA coh1_ai1.seq
1499  GCGCAACGGGGTGGTACTACCAAGTCGATCGTAGCTTTAGTCAACCAAAA cjb111_ai1.seq
1501  GCGCAACGGGGTGGTACTACCAAGTCGATCGTAGCTTTAGTCAACCAAAA nem316_ai1.seq
1500  GCGCAACGGGGTGGTACTACCAAGTCGATCGTAGCTTTAGTCAACCAAAA a909_ai1.seq
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FIGURE 18 AF

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      GGCGAACCGCCCAGAATGATCCAAAGGCACTAGAAAGTGTCCGTAATGAT Majority
               11560     11570     11580     11590     11600
11544 GGCGAACCGCCCAGAATGATCCAAAGGCACTAGAAAGTGTCCGTAATGAT 2603_ai1.seq
11317 GGCGAACCGCCCAGAATGATCCAAAGGCACTAGAAAGTGTCCGTAATGAT 18rs21_ai1.seq
11549 GGCGAACCGCCCAGAATGATCCAAAGGCACTAGAAAGTGTCCGTAATGAT coh1_ai1.seq
11549 GGCGAACCGCCCAGAATGATCCAAAGGCACTAGAAAGTGTCCGTAATGAT cjb111_ai1.seq
11551 GGCGAACCGCCCAGAATGATCCAAAGGCACTAGAAAGTGTCCGTAATGAT nem316_ai1.seq
11550 GGCGAACCGCCCAGAATGATCCAAAGGCACTAGAAAGTGTCCGTAATGAT a909_ai1.seq

      TCGATTTCGGGCGGTGATGATGTCATGGCTTATGCTTATAGCAAATGTAC Majority
               11610     11620     11630     11640     11650
11594 TCGATTTCGGGCGGTGATGATGTCATGGCTTATGCTTATAGCAAATGTAC 2603_ai1.seq
11367 TCGATTTCGGGCGGTGATGATGTCATGGCTTATGCTTATAGCAAATGTAC 18rs21_ai1.seq
11599 TCGATTTCGGGCGGTGATGATGTCATGGCTTATGCTTATAGCAAATGTAC coh1_ai1.seq
11599 TCGATTTCGGGCGGTGATGATGTCATGGCTTATGCTTATAGCAAATGTAC cjb111_ai1.seq
11601 TCGATTTCGGGCGGTGATGATGTCATGGCTTATGCTTATAGCAAATGTAC nem316_ai1.seq
11600 TCGATTTCGGGCGGTGATGATGTCATGGCTTATGCTTATAGCAAATGTAC a909_ai1.seq

      TTGGGGAGTTGCGGCACGAATTAATCAGTGGGACTGAAACTCAAAGGTTG Majority
               11660     11670     11680     11690     11700
1644 TTGGGGAGTTGCGGCACGAATTAATCAGTGGGACTGAAACTCAAAGGTTG 2603_ai1.seq
1417 TTGGGGAGTTGCGGCACGAATTAATCAGTGGGACTGAAACTCAAAGGTTG 18rs21_ai1.seq
1649 TTGGGGAGTTGCGGCACGAATTAATCAGTGGGACTGAAACTCAAAGGTTG coh1_ai1.seq
1649 TTGGGGAGTTGCGGCACGAATTAATCAGTGGGACTGAAACTCAAAGGTTG cjb111_ai1.seq
1651 TTGGGGAGTTGCGGCACGAATTAATCAGTGGGACTGAAACTCAAAGGTTG nem316_ai1.seq
1650 TTGGGGAGTTGCGGCACGAATTAATCAGTGGGACTGAAACTCAAAGGTTG a909_ai1.seq

      AAATGGTGAGAAGATTACCATTACCAGTTCAATGGGAAATGGTCAGGATT Majority
               11710     11720     11730     11740     11750
1694 AAATGGTGAGAAGATTACCATTACCAGTTCAATGGGAAATGGTCAGGATT 2603_ai1.seq
1467 AAATGGTGAGAAGATTACCATTACCAGTTCAATGGGAAATGGTCAGGATT 18rs21_ai1.seq
1699 AAATGGTGAGAAGATTACCATTACCAGTTCAATGGGAAATGGTCAGGATT coh1_ai1.seq
1699 AAATGGTGAGAAGATTACCATTACCAGTTCAATGGGAAATGGTCAGGATT cjb111_ai1.seq
1701 AAATGGTGAGAAGATTACCATTACCAGTTCAATGGGAAATGGTCAGGATT nem316_ai1.seq
1700 AAATGGTGAGAAGATTACCATTACCAGTTCAATGGGAAATGGTCAGGATT a909_ai1.seq

      GGGTTGGAACAGCCGAAAGACTAGATGGTGAAACTGATACAGTTCCAAAA Majority
               11760     11770     11780     11790     11800
1744 GGGTTGGAACAGCCGAAAGACTAGATGGTGAAACTGATACAGTTCCAAAA 2603_ai1.seq
1517 GGGTTGGAACAGCCGAAAGACTAGATGGTGAAACTGATACAGTTCCAAAA 18rs21_ai1.seq
1749 GGGTTGGAACAGCCGAAAGACTAGATGGTGAAACTGATACAGTTCCAAAA coh1_ai1.seq
1749 GGGTTGGAACAGCCGAAAGACTAGATGGTGAAACTGATACAGTTCCAAAA cjb111_ai1.seq
1751 GGGTTGGAACAGCCGAAAGACTAGATGGTGAAACTGATACAGTTCCAAAA nem316_ai1.seq
1750 GGGTTGGAACAGCCGAAAGACTAGATGGTGAAACTGATACAGTTCCAAAA a909_ai1.seq

      GAAGGTACTATTCTCTCTTTTTAGGAAAGTAGTTATGGTTCGTATATAGG Majority
               11810     11820     11830     11840     11850
794 GAAGGTACTATTCTCTCTTTTTAGGAAAGTAGTTATGGTTCGTATATAGG 2603_ai1.seq
567 GAAGGTACTATTCTCTCTTTTTAGGAAAGTAGTTATGGTTCGTATATAGG 18rs21_ai1.seq
799 GAAGGTACTATTCTCTCTTTTTAGGAAAGTAGTTATGGTTCGTATATAGG coh1_ai1.seq
799 GAAGGTACTATTCTCTCTTTTTAGGAAAGTAGTTATGGTTCGTATATAGG cjb111_ai1.seq
801 GAAGGTACTATTCTCTCTTTTTAGGAAAGTAGTTATGGTTCGTATATAGG nem316_ai1.seq
800 GAAGGTACTATTCTCTCTTTTTAGGAAAGTAGTTATGGTTCGTATATAGG a909_ai1.seq

      CTACGGAACTATATCTTTCGTCACATTACATCTACAGATAGTACCATGAA Majority
               11860     11870     11880     11890     11900
844 CTACGGAACTATATCTTTCGTCACATTACATCTACAGATAGTACCATGAA 2603_ai1.seq
617 CTACGGAACTATATCTTTCGTCACATTACATCTACAGATAGTACCATGAA 18rs21_ai1.seq
849 CTACGGAACTATATCTTTCGTCACATTACATCTACAGATAGTACCATGAA coh1_ai1.seq
849 CTACGGAACTATATCTTTCGTCACATTACATCTACAGATAGTACCATGAA cjb111_ai1.seq
851 CTACGGAACTATATCTTTCGTCACATTACATCTACAGATAGTACCATGAA nem316_ai1.seq
850 CTACGGAACTATATCTTTCGTCACATTACATCTACAGATAGTACCATGAA a909_ai1.seq
```

FIGURE 18 AG

```
      TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT Majority

                11910       11920       11930       11940       11950
11894 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT 2603_all.seq
11667 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT 18rs21_all.seq
11899 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT cohl_all.seq
11899 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT cjb111_all.seq
11901 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT nem316_all.seq
11900 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT a909_all.seq

      TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT Majority

                11960       11970       11980       11990       12000
11944 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT 2603_all.seq
11717 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT 18rs21_all.seq
11949 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT cohl_all.seq
11949 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT cjb111_all.seq
11951 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT nem316_all.seq
11950 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT a909_all.seq

      GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT Majority

                12010       12020       12030       12040       12050
11994 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT 2603_all.seq
11767 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT 18rs21_all.seq
11999 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT cohl_all.seq
11999 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT cjb111_all.seq
12001 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT nem316_all.seq
12000 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT a909_all.seq

      AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG Majority

                12060       12070       12080       12090       12100
12044 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG 2603_all.seq
11817 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG 18rs21_all.seq
12049 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG cohl_all.seq
12049 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG cjb111_all.seq
12051 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG nem316_all.seq
12050 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG a909_all.seq

      CTAATAGTTCTAGAACTTCTAATTGTTTTTTCGTCGACGATATGAATTTTC Majority

                12110       12120       12130       12140       12150
2094  CTAATAGTTCTAGAACTTCTAATTGTTTTTTCGTCGACGATATGAATTTTC 2603_all.seq
1867  CTAATAGTTCTAGAACTTCTAATTGTTTTTTCGTCGACGATATGAATTTTC 18rs21_all.seq
2099  CTAATAGTTCTAGAACTTCTAATTGTTTTTTCGTCGACGATATGAATTTTC cohl_all.seq
2099  CTAATAGTTCTAGAACTTCTAATTGTTTTTTCGTCGACGATATGAATTTTC cjb111_all.seq
2101  CTAATAGTTCTAGAACTTCTAATTGTTTTTTCGTCGACGATATGAATTTTC nem316_all.seq
2100  CTAATAGTTCTAGAACTTCTAATTGTTTTTTCGTCGACGATATGAATTTTC a909_all.seq

      AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAAGGTCA Majority

                12160       12170       12180       12190       12200
2144  AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAAGGTCA 2603_all.seq
1917  AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAAGGTCA 18rs21_all.seq
2149  AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAAGGTCA cohl_all.seq
2149  AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAAGGTCA cjb111_all.seq
2151  AATCTTAACTGTTAGAATTCCACCTCCCTTTGGTTAAAGAAAAAAGGTCA nem316_all.seq
2150  AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAAGGTCA a909_all.seq

      GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT Majority

                12210       12220       12230       12240       12250
2194  GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT 2603_all.seq
1967  GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT 18rs21_all.seq
2199  GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT cohl_all.seq
2199  GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT cjb111_all.seq
2201  GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT nem316_all.seq
2200  GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT a909_all.seq
```

FIGURE 18 AH

```
      TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG Majority
               12260     12270     12280     12290     12300
12244 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG 2603_ai1.seq
12017 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG 18rs21_ai1.seq
12249 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG coh1_ai1.seq
12249 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG cjb111_ai1.seq
12251 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG nem316_ai1.seq
12250 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG a909_ai1.seq

      AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAAATGCT Majority
               12310     12320     12330     12340     12350
12294 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAAATGCT 2603_ai1.seq
12067 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAAATGCT 18rs21_ai1.seq
12299 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAAATGCT coh1_ai1.seq
12299 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAAATGCT cjb111_ai1.seq
12301 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAAATGCT nem316_ai1.seq
12300 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAAATGCT a909_ai1.seq

      CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAAATTGA Majority
               12360     12370     12380     12390     12400
2344  CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAAATTGA 2603_ai1.seq
2117  CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAAATTGA 18rs21_ai1.seq
2349  CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAAATTGA coh1_ai1.seq
2349  CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAAATTGA cjb111_ai1.seq
2351  CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAAATTGA nem316_ai1.seq
2350  CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAAATTGA a909_ai1.seq

      ACTTGATAATCGGTTGTCTCCGACTGAACAAAAGTTATTGATTACCTTAT Majority
               12410     12420     12430     12440     12450
2394  ACTTGATAATCGGTTGTCTCCGACTGAAAAAAAGTTATTGATTACCTTAT 2603_ai1.seq
2167  ACTTGATAATCGGTTGTCTCCGACTGAACAAAAGTTATTGATTACCTTAT 18rs21_ai1.seq
2399  ACTTGATAATCGGTTGTCTCCGACTGAACAAAAGTTATTGATTACCTTAT coh1_ai1.seq
2399  ACTTGATAATCGGTTGTCTCCGACTGAACAAAAGTTATTGATTACCTTAT cjb111_ai1.seq
2401  ACTTGATAATCGGTTGTCTCCGACTGAACAAAAGTTATTGATTACCTTAT nem316_ai1.seq
2400  ACTTGATAATCGGTTGTCTCCGACTGAACAAAAGTTATTGATTACCTTAT a909_ai1.seq

      TATTACATACTAAAGGTTTAATCATTGATATGTAAGAAGTAAGTCAGCTA Majority
               12460     12470     12480     12490     12500
2444  TATTACATACTAAAGGTTTAATCATTGATATGTAAGAAGTAAGTCAGCTA 2603_ai1.seq
2217  TATTACATACTAAAGGTTTAATCATTGATATGTAAGAAGTAAGTCAGCTA 18rs21_ai1.seq
2449  TATTACATACTAAAGGTTTAATCATTGATATGTAAGAAGTAAGTCAGCTA coh1_ai1.seq
2449  TATTACATACTAAAGGTTTAATCATTGATATGTAAGAAGTAAGTCAGCTA cjb111_ai1.seq
2451  TATTACATACTAAAGGTTTAATCATTGATATGTAAGAAGTAAGTCAGCTA nem316_ai1.seq
2450  TATTACATACTAAAGGTTTAATCATTGATATGTAAGAAGTAAGTCAGCTA a909_ai1.seq

      ACCGATCTTTCTATTCTAAAACTTATATTGTTGCTTTAGAAATTTTAAAG Majority
               12510     12520     12530     12540     12550
2494  ACCGATCTTTCTATTCTAAAACTTATATTGTTGCTTTAGAAATTTTAAAG 2603_ai1.seq
2267  ACCGATCTTTCTATTCTAAAACTTATATTGTTGCTTTAGAAATTTTAAAG 18rs21_ai1.seq
2499  ACCGATCTTTCTATTCTAAAACTTATATTGTTGCTTTAGAAATTTTAAAG coh1_ai1.seq
2499  ACCGATCTTTCTATTCTAAAACTTATATTGTTGCTTTAGAAATTTTAAAG cjb111_ai1.seq
2501  ACCGATCTTTCTATTCTAAAACTTATATTGTTGCTTTAGAAATTTTAAAG nem316_ai1.seq
2500  ACCGATCTTTCTATTCTAAAACTTATATTGTTGCTTTAGAAATTTTAAAG a909_ai1.seq

      AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA Majority
               12560     12570     12580     12590     12600
2544  AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA 2603_ai1.seq
2317  AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA 18rs21_ai1.seq
2549  AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA coh1_ai1.seq
2549  AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA cjb111_ai1.seq
2551  AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA nem316_ai1.seq
2550  AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA a909_ai1.seq
```

FIGURE 18 AI

```
     AAAAATATGATATTTGAAGAGTCCAAAGATCTAATAGATAGTCCAGTTAG Majority
         12610     12620     12630     12640     12650
2594 AAAAATATGATATTTGAAGAGTCCAAAGATCTAATAGATAGTCCAGTTAG 2603_ail.seq
2367 AAAAATATGATATTTGAAGAGTCCAAAGATCTAATAGATAGTCCAGTTAG 18rs21_ail.seq
2599 AAAAATATGATATTTGAAGAGTCCAAAGATCTAATAGATAGTCCAGTTAG cohl_ail.seq
2599 AAAAATATGATATTTGAAGAGTCCAAAGATCTAATAGATAGTCCAGTTAG cjb111_ail.seq
2601 AAAAATATGATATTTGAAGAGTCCAAAGATCTAATAGATAGTCCAGTTAG nem316_ail.seq
2600 AAAAATATGATATTTGAAGAGTCCAAAGATCTAATAGATAGTCCAGTTAG a909_ail.seq

     AGAAGCGTTGATTATAAGTGATAAGGATTTTCAAAAATTAAAACAAGAGC Majority
         12660     12670     12680     12690     12700
2644 AGAAGCGTTGATTATAAGTGATAAGGATTTTCAAAAATTAAAACAAGAGC 2603_ail.seq
2417 AGAAGCGTTGATTATAAGTGATAAGGATTTTCAAAAATTAAAACAAGAGC 18rs21_ail.seq
2649 AGAAGCGTTGATTATAAGTGATAAGGATTTTCAAAAATTAAAACAAGAGC cohl_ail.seq
2649 AGAAGCGTTGATTATAAGTGATAAGGATTTTCAAAAATTAAAACAAGAGC cjb111_ail.seq
2651 AGAAGCGTTGATTATAAGTGATAAGGATTTTCAAAAATTAAAACAAGAGC nem316_ail.seq
2650 AGAAGCGTTGATTATAAGTGATAAGGATTTTCAAAAATTAAAACAAGAGC a909_ail.seq

     TATTATTTTAACCGACTTATTTTAAAGACTTATCATATCTAGGCTTGCTT Majority
         12710     12720     12730     12740     12750
2694 TATTATTTTAACCGACTTATTTTAAAGACTTATCATATCTAGGCTTGCTT 2603_ail.seq
2467 TATTATTTTAACCGACTTATTTTAAAGACTTATCATATCTAGGCTTGCTT 18rs21_ail.seq
2699 TATTATTTTAACCGACTTATTTTAAAGACTTATCATATCTAGGCTTGCTT cohl_ail.seq
2699 TATTATTTTAACCGACTTATTTTAAAGACTTATCATATCTAGGCTTGCTT cjb111_ail.seq
2701 TATTATTTTAACCGACTTATTTTAAAGACTTATCATATCTAGGCTTGCTT nem316_ail.seq
2700 TATTATTTTAACCGACTTATTTTAAAGACTTATCATATCTAGGCTTGCTT a909_ail.seq

     GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA Majority
         12760     12770     12780     12790     12800
2744 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA 2603_ail.seq
2517 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA 18rs21_ail.seq
2749 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA cohl_ail.seq
2749 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA cjb111_ail.seq
2751 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA nem316_ail.seq
2750 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA a909_ail.seq

     AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG Majority
         12810     12820     12830     12840     12850
2794 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG 2603_ail.seq
2567 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG 18rs21_ail.seq
2799 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG cohl_ail.seq
2799 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG cjb111_ail.seq
2801 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG nem316_ail.seq
2800 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG a909_ail.seq

     AGATTTGGAATTATGAACCAATCCCTTTGATTACTAGAAAAATAAATAGC Majority
         12860     12870     12880     12890     12900
2844 AGATTTGGAATTATGAACCAATCCCTTTGATTACTAGAAAAATAAATAGC 2603_ail.seq
2617 AGATTTGGAATTATGAACCAATCCCTTTGATTACTAGAAAAATAAATAGC 18rs21_ail.seq
2849 AGATTTGGAATTATGAACCAATCCCTTTGATTACTAGAAAAATAAATAGC cohl_ail.seq
2849 AGATTTGGAATTATGAACCAATCCCTTTGATTACTAGAAAAATAAATAGC cjb111_ail.seq
2851 AGATTTGGAATTATGAACCAATCCCTTTGATTACTAGAAAAATAAATAGC nem316_ail.seq
2850 AGATTTGGAATTATGAACCAATCCCTTTGATTACTAGAAAAATAAATAGC a909_ail.seq

     TTGGAGAGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTTAACA Majority
         12910     12920     12930     12940     12950
2894 TTGGAGAGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTTAACA 2603_ail.seq
2667 TTGGAGAGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTTAACA 18rs21_ail.seq
2899 TTGGAGAGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTTAACA cohl_ail.seq
2899 TTGGAGAGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTTAACA cjb111_ail.seq
2901 TTGGAGAGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTTAACA nem316_ail.seq
2900 TTGGAGAGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTTAACA a909_ail.seq
```

FIGURE 18 AJ

```
      C T A A G A A T G A T G A A G A C C C T C G T A T T G A A G A A G A A G T T G A G C A G C T A G A A  Majority
                     12960         12970         12980         12990         13000
12944 C T A A G A A T G A T G A A G A C C C T C G T A T T G A A G A A G A A G T T G A G C A G C T A G A A  2603_all.seq
12717 C T A A G A A T G A T G A A G A C C C T C G T A T T G A A G A A G A A G T T G A G C A G C T A G A A  18rs21_all.seq
12949 C T A A G A A T G A T G A A G A C C C T C G T A T T G A A G A A G A A G T T G A G C A G C T A G A A  coh1_all.seq
12949 C T A A G A A T G A T G A A G A C C C T C G T A T T G A A G A A G A A G T T G A G C A G C T A G A A  cjb111_all.seq
12951 C T A A G A A T G A T G A A G A C C C T C G T A T T G A A G A A G A A G T T G A G C A G C T A G A -  nem316_all.seq
12950 C T A A G A A T G A T G A A G A C C C T C G T A T T G A A G A A G A A G T T G A G C A G C T A G A A  a909_all.seq

      G A T A A G A T                                                                              Majority

12994 G A T A A G A T                                                                              2603_all.seq
12767 G A T A A G A T                                                                              18rs21_all.seq
12999 G A T A A G A T                                                                              coh1_all.seq
12999 G A                                                                                          cjb111_all.seq
13000 - A                                                                                          nem316_all.seq
13000 G A T A A G A T                                                                              a909_all.seq
```

Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

FIGURE 18 AK

Start	Sequence	Name
	GGCCTTGTTCCGATGTTGATCCCGATAACTCCTGGCTCATTAATAGCCTG	Majority
	10 20 30 40 50	
1	GGCCTTGTTCCGATGTTGATTCCGATAACTCCTGGCTCATTAATAGCCTG	2603_a12.seq
1	GGCCTTGTTCCGATGTTGATTCCGATAACTCCTGGCTCATTAATAGCCTG	18rs21_a12.seq
1	GGCCTTGTTCCGATGTTGATCCCGATAACTCCTGGCTCATTAATAGCCTG	515_a12.seq
1	GGCCTTGTTCCGATGTTGATCCCGATAACTCCTGGCTCATTAATAGCCTG	cjb111_a12.seq
1	GGCCTTGTTCCGATGTTGATCCCGATAACTCCTGGCTCATTAATAGCCTG	h36b_a12.seq
	TTCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAAT	Majority
	60 70 80 90 100	
51	TTCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAAT	2603_a12.seq
51	TTCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAAT	18rs21_a12.seq
51	TTCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAAT	515_a12.seq
51	TTCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAAT	cjb111_a12.seq
51	TTCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAAT	h36b_a12.seq
	TTTGAAAATAGACTAAGTATTTATTAACCTCAGGCCACTTTCTATGCATG	Majority
	110 120 130 140 150	
101	TTTGAAAATAGACTAAGTATTTATTAACCTCAGGCCACTTTCTATGCATG	2603_a12.seq
101	TTTGAAAATAGACTAAGTATTTATTAACCTCAGGCCACTTTCTATGCATG	18rs21_a12.seq
101	TTTGAAAATAGACTAAGTATTTATTAACTTCAGGCCACTTTCTATGCATG	515_a12.seq
101	TTTGAAAATAGACTAAGTATTTATTAACCTCAGGCCACTTTCTATGCATG	cjb111_a12.seq
101	TTTGAAAATAGACTAAGTATTTATTAACCTCAGGCCACTTTCTATGCATG	h36b_a12.seq
	AAATCAATTTCTTTATAGAATTGTTCACGAATAGGAGCTTCTGGAGCAAC	Majority
	160 170 180 190 200	
151	AAATCAATTTCTTTATAGAATTGTTCACGAATAGGAGCTTCTGGAGCAAC	2603_a12.seq
151	AAATCAATTTCTTTATAGAATTGTTCACGAATAGGAGCTTCTGGAGCAAC	18rs21_a12.seq
151	AAATCAATTTCTTTATAGAATTGTTCACGAATAGGAGCTTCTGGAGCAAC	515_a12.seq
151	AAATCAATTTCTTTATAGAATTGTTCACGAATAGGAGCTTCTGGAGCAAC	cjb111_a12.seq
151	AAATCAATTTCTTTATAGAATTGTTCACGAATAGGAGCTTCTGGAGCAAC	h36b_a12.seq
	TATAGCATCCCCTGAACCAGAAACTGTGCAAAAAGTGCACCCTCCTCTAG	Majority
	210 220 230 240 250	
201	TATAGCATCCCCTGAACCAGAAACTGTGCAAAAAGTGCACCCTCCTCTAG	2603_a12.seq
201	TATAGCATCCCCTGAACCAGAAACTGTGCAAAAAGTGCACCCTCCTCTAG	18rs21_a12.seq
201	TATAGCATCCCCTGAACCAGAAACTGTGCAAAAAGTGCACCCTCCTCTAG	515_a12.seq
201	TATAGCATCCCCTGAACCAGAAACTGTGCAAAAAGTGCACCCTCCTCTAG	cjb111_a12.seq
201	TATAGCATCCCCTGAACCAGAAACTGTGCAAAAAGTGCACCCTCCTCTAG	h36b_a12.seq
	CAACTGTTCCGTCTCTGTTAGGACAGTCAAAACCAGCATCTATAGGTAAT	Majority
	260 270 280 290 300	
251	CAACTGTTCCGTCTCTGTTAGGACAGTCAAAACCAGCATCTATAGGTAAT	2603_a12.seq
251	CAACTGTTCCGTCTCTGTTAGGACAGTCAAAACCAGCATCTATAGGTAAT	18rs21_a12.seq
251	CAACTGTTCCGTCTCTGTTAGGACAGTCAAAACCAGCATCTATAGGTAAT	515_a12.seq
251	CAACTGTTCCATCTCTGTTAGGACAGTCAAAACCAGCATCTATAGGTAAT	cjb111_a12.seq
251	CAACTGTTCCGTCTCTGTTAGGACAGTCAAAACCAGCATCTATAGGTAAT	h36b_a12.seq
	TTAAATATTTTTTCTCCAAAGAGTTCTCGATAATAATCATTAATCGCACG	Majority
	310 320 330 340 350	
301	TTAAATATTTTTTCTCCAAAGAGTTCTCGATAATAATCATTAATCGCACG	2603_a12.seq
301	TTAAATATTTTTTCTCCAAAGAGTTCTCGATAATAATCATTAATCGCACG	18rs21_a12.seq
301	TTAAATATTTTTTCTCCAAAGAGTTCTCGATAATAATCATTAATCGCACG	515_a12.seq
301	TTAAATATTTTTTCTCCAAAGAGTTCTCGATAATAATCATTAATCGCACG	cjb111_a12.seq
301	TTAAATATTTTTTCTCCAAAGAGTTCTCGATAATAATCATTAATCGCACG	h36b_a12.seq
	ATAACGTTTTTTCATAGGATAATTGTATCACAATTTTAACTAAAATAACC	Majority
	360 370 380 390 400	
351	ATAACGTTTTTTCATAGGATAATTGTATCACAATTTTAACTAAAATAACC	2603_a12.seq
351	ATAACGTTTTTTCATAGGATAATTGTATCACAATTTTAACTAAAATAACC	18rs21_a12.seq
351	ATAACGTTTTTTCATAGGATAATTGTATCACAATTTTAACTAAAATAACC	515_a12.seq
351	ATAACGTTTTTTCATAGGATAATTGTATCACAATTTTAACTAAAATAACC	cjb111_a12.seq
351	ATAACGTTTTTTCATAGGATAATTGTATCACAATTTTAACTAAAATAACC	h36b_a12.seq
	TCACTACTACAATAAAACTAAAAAAGATTGGAACGTCAGTTAGTCCCAAT	Majority
	410 420 430 440 450	
401	TCACTACTACAATAAAACTAAAAAAGATTGGAACGTCAGTTAGTCCCAAT	2603_a12.seq
401	TCACTACTACAATAAAACTAAAAAAGATTGGAACGTCAGTTAGTCCCAAT	18rs21_a12.seq
401	TCACTACTACAATAAAACTAAAAAAGATTGGAACATCAGTTAGTCCCAAT	515_a12.seq
401	TCACTACTACAATAAAACTAAAAAAGATTGGAACTAACTGACGTTCCAAT	cjb111_a12.seq
401	TCACTACTACAATAAAACTAAAAAAGATTGGAACGTCAGTTAGTCCCAAT	h36b_a12.seq

Figure 19

```
    CTTTTATTTACTTCACTTTCTTTAACCAATCCTTGGCTAAAAAGATATAC Majority
         460       470       480       490       500
451 CTTTTATTTACTTCACTTTCTTTAACCAATCCTTGGCTAAAAAGATATAC 2603_al2.seq
451 CTTTTATTTACTTCACTTTCTTTAACCAATCCTTGGCTAAAAAGATATAC 18rs21_al2.seq
451 CTTTTATTTACTTCACTTTCTTTAACCAATCCTTGGCTAAAAAGATATAC 515_al2.seq
451 CTTTTATTTACTTCACTTTCTTTAACCAATCCTTGGCTAAAAAGATATAC cjb111_al2.seq
451 CTTTTATTTACTTCACTTTCTTTAACCAATCCTTGGCTAAAAAGATATAC h36b_al2.seq

    GCAGTTAGATTCAAAATACCATAAGCAAGTATAAAACCAGCTAAAACATC Majority
         510       520       530       540       550
501 GCAGTTAGATTCAAAATACCATAAGCAAGTATAAAACCAGCTAAAACATC 2603_al2.seq
501 GCAGTTAGATTCAAAATACCATAAGCAAGTATAAAACCAGCTAAAACATC 18rs21_al2.seq
501 GCAGTTAGATTCAAAATACCATAAGCAAGTATAAAACCAGCTAAAACATC 515_al2.seq
501 GCAGTTAGATTCAAAATACCATAAGCAAGTATAAAACCAGCTAAAACATC cjb111_al2.seq
501 GCAGTTAGATTCAAAATACCATAAGCAAGTATAAAACCAGCTAAAACATC h36b_al2.seq

    TGTCGGAAAATGAACCCCTAGGTAAATACGAGATAACCCAATTAAAAAAA Majority
         560       570       580       590       600
551 TGTCGGAAAATGAACCCCTAGGTAAATACGAGATAACCCAATTAAAAAAA 2603_al2.seq
551 TGTCGGAAAATGAACCCCTAGGTAAATACGAGATAACCCAATTAAAAAAA 18rs21_al2.seq
551 TGTCGGAAAATGAACCCCTAGGTAAATACGAGATAACCCAATTAAAAAAA 515_al2.seq
551 TGTCGGAAAATGAACCCCTAGGTAAATACGAGATAACCCAATTAAAAAAA cjb111_al2.seq
551 TGTCGGAAAATGAACCCCTAGGTAAATACGAGATAACCCAATTAAAAAAA h36b_al2.seq

    TGAGCAAACCCAAAGTACCTTGGCACAACAGTTTCCATATACTCTTAGGC Majority
         610       620       630       640       650
601 TGAGCAAACCCAAAGTACCTTGGCACAACAGTTTCCATATACTCTTAGGC 2603_al2.seq
601 TGAGCAAACCCAAAGTACCTTGGCACAACAGTTTCCATATACTCTTAGGC 18rs21_al2.seq
601 TGAGCAAACCCAAAATACCTTGGCACAACAGTTTCCATATACTATTAGGC 515_al2.seq
601 TGAGCAAACCCAAAATACCTTGGTACAACAGTTTCCATATACTCTTAGGC cjb111_al2.seq
601 TGAGCAAACCCAAAGTACCTTGGCACAACAGTTTCCATATACTCTTAGGC h36b_al2.seq

    ATATAGTACTGCAATAAAATAATAATACTCCCAAATATCATAAATGTTCC Majority
         660       670       680       690       700
651 ATATAGTACTGCAATAAAATAATAATACTCCCAAATATCATAAATGTTCC 2603_al2.seq
651 ATATAGTACTGCAATAAAATAATAATACTCCCAAATATCATAAATGTTCC 18rs21_al2.seq
651 ATATAGTACTGCAATAAAATAATAATACTCCCAAATATCATAAATGTTCC 515_al2.seq
651 ATATAGTACTGCAATAAGATAATAATACTCCCAAATATCATAAATGTTCC cjb111_al2.seq
651 ATATAGTACTGCAATAAAATAATAATACTCCCAAATATCATAAATGTTCC h36b_al2.seq

    CATCGAGTGCCCACTGGGAAACGAATAGCCACCTGCAAATACTAAATGGG Majority
         710       720       730       740       750
701 CATCGAGTGCCCACTGGGAAACGAATAGCCACCTGCAAATACTAAATGGG 2603_al2.seq
701 CATCGAGTGCCCACTGGGAAACGAATAGCCACCTGCAAATACTAAATGGG 18rs21_al2.seq
701 CATCGAGTGCCCACTGGGAAACGAATAGCCACCTGCAAATACTAAATGGG 515_al2.seq
701 CATCGAGTGCCCACTGGGAAACGAATAGCCACCTGCAAATACTAAATGGG cjb111_al2.seq
701 CATCGAGTGCCCACTGGGAAACGAATAGCCACCTGCAAATACTAAATGGG h36b_al2.seq

    TTAAAGTTGGTCTTACTCTTTGAAAAATAAGTTTTAAAGAAAGTATACAT Majority
         760       770       780       790       800
751 TTAAAGTTGGTCTTACTCTTTGAAAAATAAGTTTTAAAGAAAGTATACAT 2603_al2.seq
751 TTAAAGTTGGTCTTACTCTTTGAAAAATAAGTTTTAAAGAAAGTATACAT 18rs21_al2.seq
751 GTAAAGTTGGTCTTACTCTTTGAAAAATAAGTTTTAAAGAAAGTATACAT 515_al2.seq
751 TTAAAGTTGGTCTTACTCTTTGAAAAATAAGTTTTAAAGAAAGTATACAT cjb111_al2.seq
751 TTAAAGTTGGTCTTACTCTTTGAAAAATAAGTTTTAAAGAAAGTATACAT h36b_al2.seq

    ATACCAGAGATAATAGCATTTACTGCGATAAATCTAGCTTGAGGATACCA Majority
         810       820       830       840       850
801 ATACCAGAGATAATAGCATTTACTGCGATAAATCTAGCTTGAGGATACCA 2603_al2.seq
801 ATACCAGAGATAATAGCATTTACTGCGATAAATCTAGCTTGAGGATACCA 18rs21_al2.seq
801 ATACCAGAGATAATAGCATTTACTGCGATAAATCTAGCTTGAGGATACCA 515_al2.seq
801 ATACCAGAGATAATAGCATTTACTGCGATAAATCTAGCTTGAGGATACCA cjb111_al2.seq
801 ATACCAGAGATAATAGCATTTACTGCGATAAATCTAGCTTGAGGATACCA h36b_al2.seq

    CTTCTTAAGGTAACAGAAAGTGACGCTCATAATCGCAATAGCTATCTGGC Majority
         860       870       880       890       900
851 CTTCTTAAGGTAACAGAAAGTGACGCTCATAATCGCAATAGCTATCTGGC 2603_al2.seq
851 CTTCTTAAGGTAACAGAAAGTGACGCTCATAATCGCAATAGCTATCTGGC 18rs21_al2.seq
851 CTTCTTAAGGTAACAGAAAGTGACGCTCATAATCGCAATAGCTATCTGGC 515_al2.seq
851 CTTCTTAAGGTAACAGAAAGTGACGCTCATAATCGCAATAGCTATCTGGC cjb111_al2.seq
851 CTTCTTAAGGTAACAGAAAGTGACGCTCATAATCGCAATAGCTATCTGGC h36b_al2.seq
```

FIGURE 19A

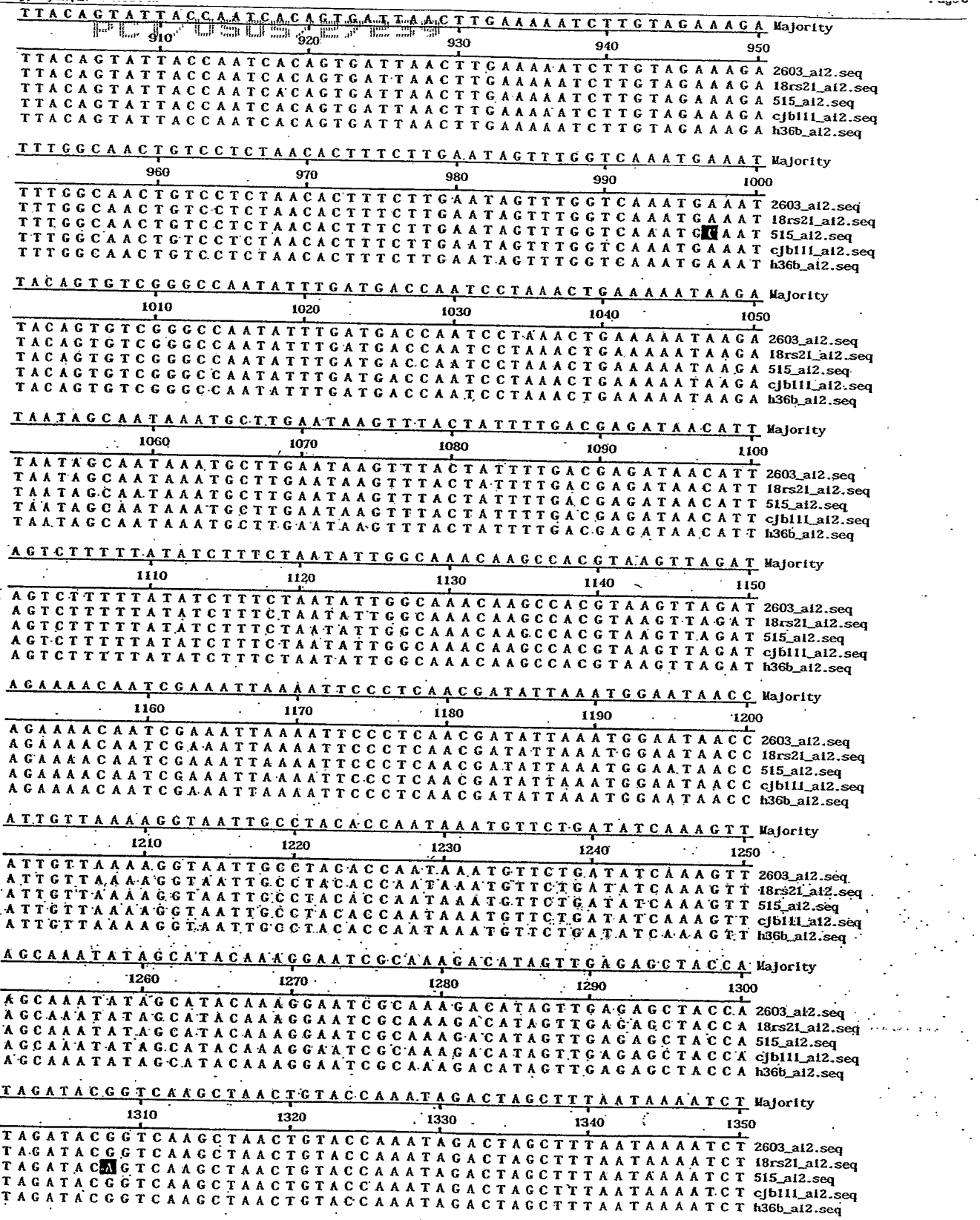
TTACAGTATTACCAATCACAGTGATTAACTTGAAAAATCTTGTAGAAAGA Majority
910 920 930 940 950
901 TTACAGTATTACCAATCACAGTGATTAACTTGAAAAATCTTGTAGAAAGA 2603_al2.seq
901 TTACAGTATTACCAATCACAGTGATTAACTTGAAAAATCTTGTAGAAAGA 18rs21_al2.seq
901 TTACAGTATTACCAATCACAGTGATTAACTTGAAAAATCTTGTAGAAAGA 515_al2.seq
901 TTACAGTATTACCAATCACAGTGATTAACTTGAAAAATCTTGTAGAAAGA cjb111_al2.seq
901 TTACAGTATTACCAATCACAGTGATTAACTTGAAAAATCTTGTAGAAAGA h36b_al2.seq
TTTGGCAACTGTCCTCTAACACTTTCTTGAATAGTTTGGTCAAATGAAAT Majority
960 970 980 990 1000
951 TTTGGCAACTGTCCTCTAACACTTTCTTGAATAGTTTGGTCAAATGAAAT 2603_al2.seq
951 TTTGGCAACTGTCCTCTAACACTTTCTTGAATAGTTTGGTCAAATGAAAT 18rs21_al2.seq
951 TTTGGCAACTGTCCTCTAACACTTTCTTGAATAGTTTGGTCAAATGCAAT 515_al2.seq
951 TTTGGCAACTGTCCTCTAACACTTTCTTGAATAGTTTGGTCAAATGAAAT cjb111_al2.seq
951 TTTGGCAACTGTCCTCTAACACTTTCTTGAATAGTTTGGTCAAATGAAAT h36b_al2.seq
TACAGTGTCGGGCCAATATTTGATGACCAATCCTAAACTGAAAAATAAGA Majority
1010 1020 1030 1040 1050
1001 TACAGTGTCGGGCCAATATTTGATGACCAATCCTAAACTGAAAAATAAGA 2603_al2.seq
1001 TACAGTGTCGGGCCAATATTTGATGACCAATCCTAAACTGAAAAATAAGA 18rs21_al2.seq
1001 TACAGTGTCGGGCCAATATTTGATGACCAATCCTAAACTGAAAAATAAGA 515_al2.seq
1001 TACAGTGTCGGGCCAATATTTGATGACCAATCCTAAACTGAAAAATAAGA cjb111_al2.seq
1001 TACAGTGTCGGGCCAATATTTGATGACCAATCCTAAACTGAAAAATAAGA h36b_al2.seq
TAATAGCAATAAATGCTTGAATAAGTTTACTATTTTGACGAGATAACATT Majority
1060 1070 1080 1090 1100
1051 TAATAGCAATAAATGCTTGAATAAGTTTACTATTTTGACGAGATAACATT 2603_al2.seq
1051 TAATAGCAATAAATGCTTGAATAAGTTTACTATTTTGACGAGATAACATT 18rs21_al2.seq
1051 TAATAGCAATAAATGCTTGAATAAGTTTACTATTTTGACGAGATAACATT 515_al2.seq
1051 TAATAGCAATAAATGCTTGAATAAGTTTACTATTTTGACGAGATAACATT cjb111_al2.seq
1051 TAATAGCAATAAATGCTTGAATAAGTTTACTATTTTGACGAGATAACATT h36b_al2.seq
AGTCTTTTTATATCTTTCTAATATTGGCAAACAAGCCACGTAAGTTAGAT Majority
1110 1120 1130 1140 1150
1101 AGTCTTTTTATATCTTTCTAATATTGGCAAACAAGCCACGTAAGTTAGAT 2603_al2.seq
1101 AGTCTTTTTATATCTTTCTAATATTGGCAAACAAGCCACGTAAGTTAGAT 18rs21_al2.seq
1101 AGTCTTTTTATATCTTTCTAATATTGGCAAACAAGCCACGTAAGTTAGAT 515_al2.seq
1101 AGTCTTTTTATATCTTTCTAATATTGGCAAACAAGCCACGTAAGTTAGAT cjb111_al2.seq
1101 AGTCTTTTTATATCTTTCTAATATTGGCAAACAAGCCACGTAAGTTAGAT h36b_al2.seq
AGAAAACAATCGAAATTAAAATTCCCTCAACGATATTAAATGGAATAACC Majority
1160 1170 1180 1190 1200
1151 AGAAAACAATCGAAATTAAAATTCCCTCAACGATATTAAATGGAATAACC 2603_al2.seq
1151 AGAAAACAATCGAAATTAAAATTCCCTCAACGATATTAAATGGAATAACC 18rs21_al2.seq
1151 AGAAAACAATCGAAATTAAAATTCCCTCAACGATATTAAATGGAATAACC 515_al2.seq
1151 AGAAAACAATCGAAATTAAAATTCCCTCAACGATATTAAATGGAATAACC cjb111_al2.seq
1151 AGAAAACAATCGAAATTAAAATTCCCTCAACGATATTAAATGGAATAACC h36b_al2.seq
ATTGTTAAAAGGTAATTGCCTACACCAATAAATGTTCTGATATCAAAGTT Majority
1210 1220 1230 1240 1250
1201 ATTGTTAAAAGGTAATTGCCTACACCAATAAATGTTCTGATATCAAAGTT 2603_al2.seq
1201 ATTGTTAAAAGGTAATTGCCTACACCAATAAATGTTCTGATATCAAAGTT 18rs21_al2.seq
1201 ATTGTTAAAAGGTAATTGCCTACACCAATAAATGTTCTGATATCAAAGTT 515_al2.seq
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FIGURE 19B

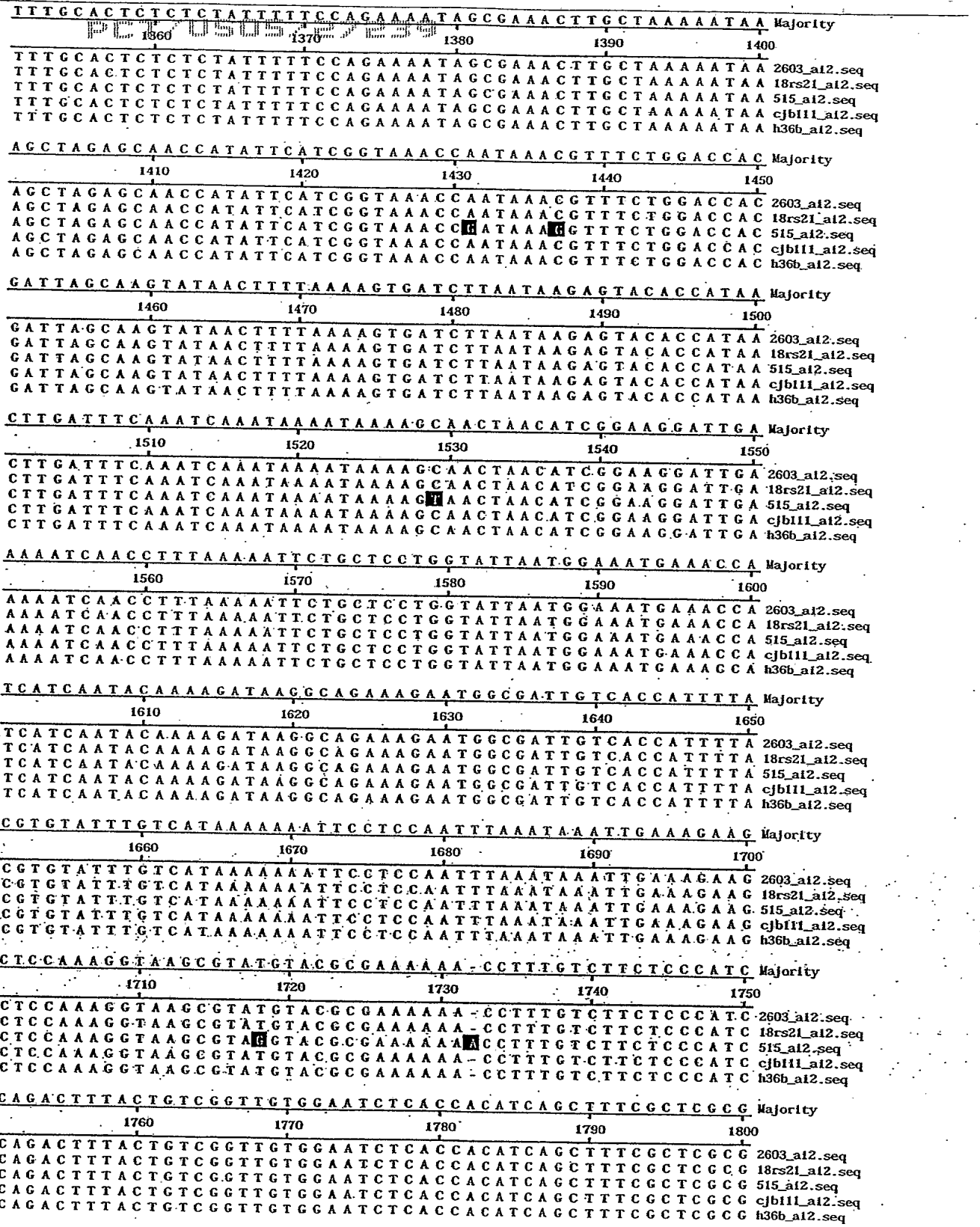
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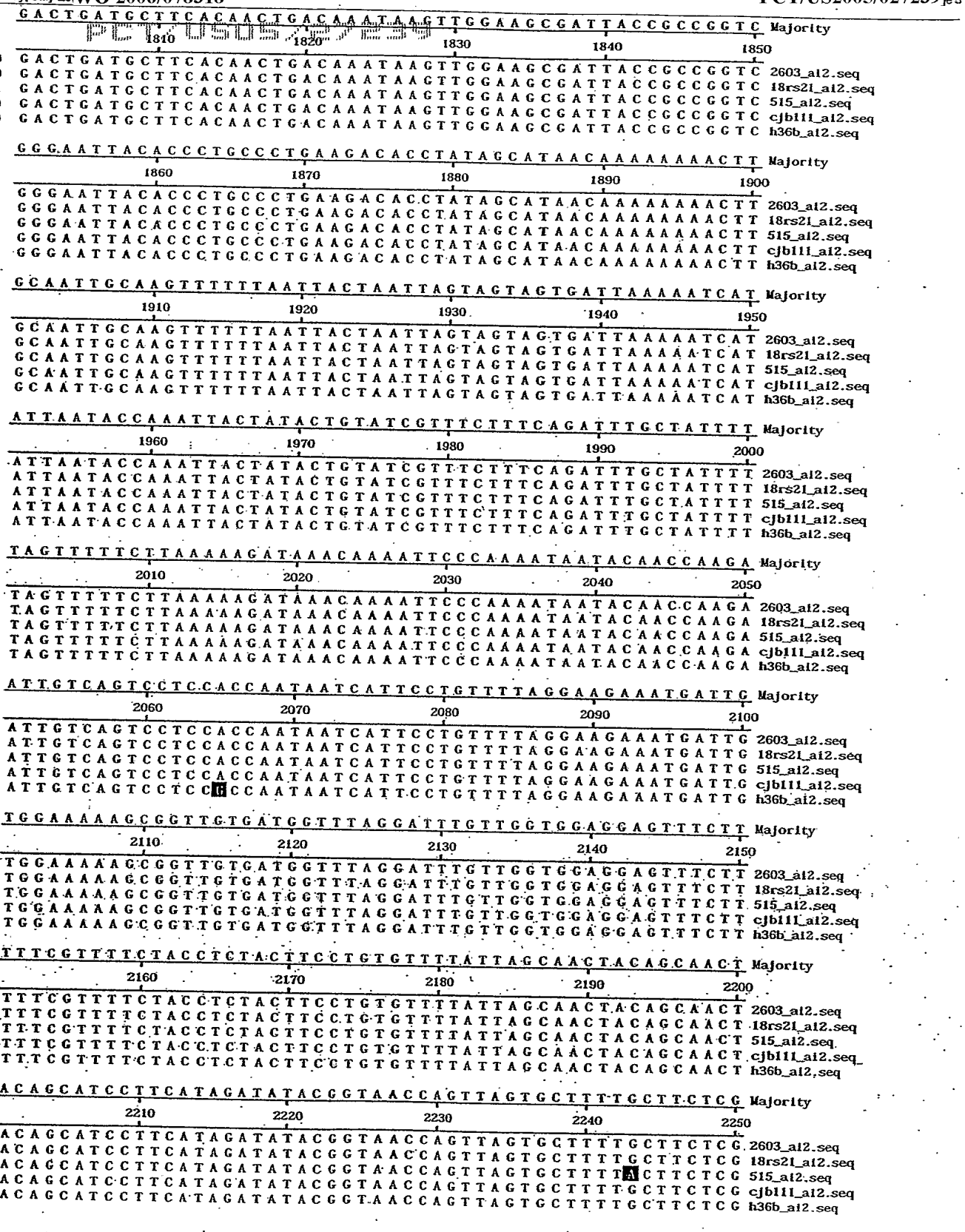
FIGURE 19C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1800 GACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTC 2603_al2.seq
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1800 GACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTC h36b_al2.seq
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1860 1870 1880 1890 1900
1850 GGGAATTACACCCTGCCCTGAAGACACCTATAGCATAACAAAAAAAACTT 2603_al2.seq
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FIGURE 19D

```
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                2260                2270                2280                2290                2300
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2250  A A A A A T A T A C T T A C C A G G T A A T A A A C C T T C A A C C T C A A T T T C T C C C T T A T 18rs21_al2.seq
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2250  A A A A A T A T A C T T A C C A G G T A A T A A A C C T T C A A C C T C A A T T T C T C C C T T A T cjb111_al2.seq
2250  A A A A A T A T A C T T A C C A G G T A A T A A A C C T T C A A C C T C A A T T T C T C C C T T A T h36b_al2.seq

      C A T C A G T T A C T A A T G A A G T A A T C C C A T C T T G A T C G G T C G T A A A T C G T C C A Majority
                2310                2320                2330                2340                2350
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      T T T T T A A A G C G A A C T G G C T G A T T C T G G T T A T C G T A T A A T A C A A A T A T T A C Majority
                2360                2370                2380                2390                2400
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      T T A A T C G G C C T G T T T C A A C T T T T C G C T T A G G A T T T A T C T G T A A T T G A T T T Majority
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                2510                2520                2530                2540                2550
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      G C T T T G A T C A G C T T T A T A A G C A C G A C C A A A G T A C G A A C C A T T T G G G A G T G Majority
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      T A C T T C T G G T T C A A T T C G C T A T C T G T C A T T T G G C T C A A T A A A T C A A C T T T Majority
                2660                2670                2680                2690                2700
2650  T A C T T C T G G T T C A A T T C G C T A T C T G T C A T T T G G C T C A A T A A A T C A A C T T T 2603_al2.seq
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FIGURE 19E

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     TATTTGGCTGAAGTCCTATCTGTGTGATTGTTAGTTGATTAGGGGTATCA Majority
              2760      2770      2780      2790      2800
2750 TATTTGGCTGAAGTCCTATCTGTGTGATTGTTAGTTGATTAGGGGTATCA 2603_al2.seq
2750 TATTTGGCTGAAGTCCTATCTGTGTGATTGTTAGTTGATTAGGGGTATCA 18rs21_al2.seq
2751 TATTTGGCTGAAGTCCTATCTGTGTGATTGTTAGTTGATTAGGGGTATCA 515_al2.seq
2750 TATTTGGCTGAAGTCCTATCTGTGTGATTGTTAGTTGATTAGGGGTATCA cjb111_al2.seq
2750 TATTTGGCTGAAGTCCTATCTGTGTGATTGTTAGTTGATTAGGGGTATCA h36b_al2.seq

     GCATTTACACTGGCTACCGAAAAAAACGCTAATTGTACCAATCCTAAAAA Majority
              2810      2820      2830      2840      2850
2800 GCATTTACACTGGCTACCGAAAAAAACGCTAATTGTACCAATCCTAAAAA 2603_al2.seq
2800 GCATTTACACTGGCTACCGAAAAAAACGCTAATTGTACCAATCCTAAAAA 18rs21_al2.seq
2801 GCATTTACACTGGCTACCGAAAAAAACGCTAATTGTACCAATCCTAAAAA 515_al2.seq
2800 GCATTTACACTGGCTACCGAAAAAAACGCTAATTGTACCAATCCTAAAAA cjb111_al2.seq
2800 GCATTTACACTGGCTACCGAAAAAAACGCTAATTGTACCAATCCTAAAAA h36b_al2.seq

     GCAACATAGTAGAAGTCCTAAACTTTTTCTAATCTTTTTCATTTTTGATT Majority
              2860      2870      2880      2890      2900
2850 GCAACATAGTAGAAGTCCTAAACTTTTTCTAATCTTTTTCATTTTTGATT 2603_al2.seq
2850 GCAACATAGTAGAAGTCCTAAACTTTTTCTAATCTTTTTCATTTTTGATT 18rs21_al2.seq
2851 GCAACATAGTAGAAGTCCTAAACTTTTTCTAATCTTTTTCATTTTTGATT 515_al2.seq
2850 GCAACATAGTAGAAGTCCTAAACTTTTTCTAATCTTTTTCATTTTTGATT cjb111_al2.seq
2850 GCAACATAGTAGAAGTCCTAAACTTTTTCTAATCTTTTTCATTTTTGATT h36b_al2.seq

     TCCCTTTCTCTTTCTCTCTTTAAATTTTCGTTTTAAATATAATAGTAAAG Majority
              2910      2920      2930      2940      2950
2900 TCCCTTTCTCTTTCTCTCTTTAAATTTTCGTTTTAAATATAATAGTAAAG 2603_al2.seq
2900 TCCCTTTCTCTTTCTCTCTTTAAATTTTCGTTTTAAATATAATAGTAAAG 18rs21_al2.seq
2901 TCCCTTTCTCTTTCTCTCTTTAAATTTTCGTTTTAAATATAATAGTAAAG 515_al2.seq
2900 TCCCTTTCTCTTTCTCTCTTTAAATTTTCGTTTTAAATATAATAGTAAAG cjb111_al2.seq
2900 TCCCTTTCTTTTTCTCTCTTTAAATTTTCGTTTTAAATATAATAGTAAAG h36b_al2.seq

     CGACTAATATAAGAATAACTAGGATTGATAAGAGGAAATAAAGTTTATAG Majority
              2960      2970      2980      2990      3000
2950 CGACTAATATAAGAATAACTAGGATTGATAAGAGGAAATAAAGTTTATAG 2603_al2.seq
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2950 CGACTAATATAAGAATAACTAGGATTGATAAGAGGAAATAAAGTTTATAG cjb111_al2.seq
2950 CGACTAATATAAGAATAACTAGGATTGATAAGAGGAAATAAAGTTTATAG h36b_al2.seq

     TGTGTTTGCAATTCTTTCATTAAATAGTTCTTTTCTTTAACAGGAGGTAC Majority
              3010      3020      3030      3040      3050
3000 TGTGTTTGCAATTCTTTCATTAAATAGTTCTTTTCTTTAACAGGAGGTAC 2603_al2.seq
3000 TGTGTTTGCAATTCTTTCATTAAATAGTTCTTTTCTTTAACAGGAGGTAC 18rs21_al2.seq
3001 TGTGTTTGCAATTCTTTCATTAAATAGTTCTTTTCTTTAACAGGAGGTAC 515_al2.seq
3000 TGTGTTTGCAATTCTTTCATTAAATAGTTCTTTTCTTTAACAGGAGGTAC cjb111_al2.seq
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     ATACTTGATTCGATGCCCTCTAACTAGTAAACGATGTGAATTAATCGAAT Majority
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3050 ATACTTGATTCGATGCCCTCTAACTAGTAAACGATGTGAATTAATCGAAT 18rs21_al2.seq
3051 ATACTTGATTCGATGCCCTCTAACTAGTAAACGATGTGAATTAATCGAAT 515_al2.seq
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3050 ATACTTGATTCGATGCCCTCTAACTAGTAAACGATGTGAATTAATCGAAT h36b_al2.seq

     AAGGTGTACATGTTAGCAAAGTCGCATAATCCTTACCTTTAACAACCAAT Majority
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3100 AAGGTGTACATGTTAGCAAAGTCGCATAATCCTTACCTTTAACAACCAAT 2603_al2.seq
3100 AAGGTGTACATGTTAGCAAAGTCGCATAATCCTTACCTTTAACAACCAAT 18rs21_al2.seq
3101 AAGGTGTACATGTTAGCAAAGTCGCATAATCCTTACCTTTAACAACCAAT 515_al2.seq
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FIGURE 19F

```
     AATTTAGAAAAATTATCTGGCTTTACAACACTTATTTGATCAACCTTATA Majority
              3160      3170      3180      3190      3200
3150 AATTTAGAAAAATTATCTGGCTTTACAACACTTATTTGATCAACCTTATA 2603_a12.seq
3150 AATTTAGAAAAATTATCTGGCTTTACAACACTTATTTGATCAACCTTATA 18rs21_a12.seq
3151 AATTTAGAAAAATTATCTGGCTTTACAACACTTATTTGATCAACCTTATA 515_a12.seq
3150 AATTTAGAAAAATTATCTGGCTTTACAACACTTATTTGATCAACCTTATA cjb111_a12.seq
3150 AATTTAGAAAAATTATCTGGCTTTACAACACTTATTTGATCAACCTTATA h36b_a12.seq

     GGCTAAAACTTCTTTGATATTATGAATATAAAAAATTTTTCCTTTTTTAA Majority
              3210      3220      3230      3240      3250
3200 GGCTAAAACTTCTTTGATATTATGAATATAAAAAATTTTTCCTTTTTTAA 2603_a12.seq
3200 GGCTAAAACTTCTTTGATATTATGAATATAAAAAATTTTTCCTTTTTTAA 18rs21_a12.seq
3201 GGCTAAAACTTCTTTGATATTATGAATATAAAAAATTTTTCCTTTTTTAA 515_a12.seq
3200 GGCTAAAACTTCTTTGATATTATGAATATAAAAAATTTTTCCTTTTTTAA cjb111_a12.seq
3200 GGCTAAAACTTCTTTGATATTATGAATATAAAAAATTTTTCCTTTTTTAA h36b_a12.seq

     GTTTATCTAAATCTGTAAATAACTTAGCTTTAGGTAAGCCGCGATGAGCT Majority
              3260      3270      3280      3290      3300
3250 GTTTATCTAAATCTGTAAATAACTTAGCTTTAGGTAAGCCGCGATGAGCT 2603_a12.seq
3250 GTTTATCTAAATCTGTAAATAACTTAGCTTTAGGTAAGCCGCGATGAGCT 18rs21_a12.seq
3251 GTTTATCTAAATCTGTAAATAACTTAGCTTTAGGTAAGCCGCGATGAGCT 515_a12.seq
3250 GTTTATCTAAATCTGTAAATAACTTAGCTTTAGGTAAGCCGCGATGAGCT cjb111_a12.seq
3250 GTTTATCTAAATCTGTAAATAACTTAGCTTTAGGTAAGCCGCGATGAGCT h36b_a12.seq

     GTGATAACAGTATGTGAACTTTTTCCACCAATTGGCAAGGAGGTTCCTTC Majority
              3310      3320      3330      3340      3350
3300 GTGATAACAGTATGTGAACTTTTTCCACCAATTGGCAAGGAGGTTCCTTC 2603_a12.seq
3300 GTGATAACAGTATGTGAACTTTTTCCACCAATTGGCAAGGAGGTTCCTTC 18rs21_a12.seq
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3300 GTGATAACAGTATGTGAACTTTTTCCACCAATTGGCAAGGAGGTTCCTTC cjb111_a12.seq
3300 GTGATAACAGTATGTGAACTTTTTCCACCAATTGGCAAAGAAGTTCCTTC h36b_a12.seq

     AAGGTGTCCTGCTCCTTTTTCAAGAACACTACTGGTAGTCCCCGCATAGA Majority
              3360      3370      3380      3390      3400
3350 AAGGTGTCCTGCTCCTTTTTCAAGAACACTACTGGTAGTCCCCGCATAGA 2603_a12.seq
3350 AAGGTGTCCTGCTCCTTTTTCAAGAACACTACTGGTAGTCCCCGCATAGA 18rs21_a12.seq
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     TAGGTAATTTTTGCTTGATAGACGGTATATCAATATATCCAATCATTTCA Majority
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3400 TAGGTAATTTTTGCTTGATAGACGGTATATCAATATATCCAATCATTTCA 2603_a12.seq
3400 TAGGTAATTTTTGCTTGATAGACGGTATATCAATATATCCAATCATTTCA 18rs21_a12.seq
3401 TAGGTAATTTTTGCTTGATAGACGGTATATCAATATATCCAATCATTTCA 515_a12.seq
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     GCAATCTCAAGCATGTGGGCGTATTCAGCAATACCTTTTTTTTCTTTTTC Majority
              3460      3470      3480      3490      3500
3450 GCAATCTCAAGCATGTGGGCGTATTCAGCAATACCTTTTTTTTCTTTTTC 2603_a12.seq
3450 GCAATCTCAAGCATGTGGGCGTATTCAGCAATACCTTTTTTTTCTTTTTC 18rs21_a12.seq
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3450 GCAATCTCAAGCATGTGGGCGTATTCAGCAATACCTTTTTTTTCTTTTTC h36b_a12.seq

     AGTATAGGGATCTGATAGGCGGCTTGGGTCCAGTGTTCTATTATAAGCTT Majority
              3510      3520      3530      3540      3550
3500 AGTATAGGGATCTGATAGGCGGCTTGGGTCCAGTGTTCTATTATAAGCTT 2603_a12.seq
3500 AGTATAGGGATCTGATAGGCGGCTTGGGTCCAGTGTTCTATTATAAGCTT 18rs21_a12.seq
3501 AGTATAGGGATCTGATAGGCGGCTTGGGTCCAGTGTTCTATTATAAGCTT 515_a12.seq
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3500 AGTATAGGGATCTGATAGGCGGCTTGGGTCCAGTGTTCTATTATAAGCTT h36b_a12.seq

     TTGCTAACTCAAATCGTCTATTAATCTCTTTAGTATTTAATTTTTGGGTT Majority
              3560      3570      3580      3590      3600
3550 TTGCTAACTCAAATCGTCTATTAATCTCTTTAGTATTTAATTTTTGGGTT 2603_a12.seq
3550 TTGCTAACTCAAATCGTCTATTAATCTCTTTAGTATTTAATTTTTGGGTT 18rs21_a12.seq
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3550 TTGCTAACTCAAATCGTCTATTAATCTCTTTAGTATTTAATTTTTGGGTT cjb111_a12.seq
3550 TTGCTAACTCAAATCGTCTATTAATCTCTTTAGCATTTAATTTTTGGGTT h36b_a12.seq
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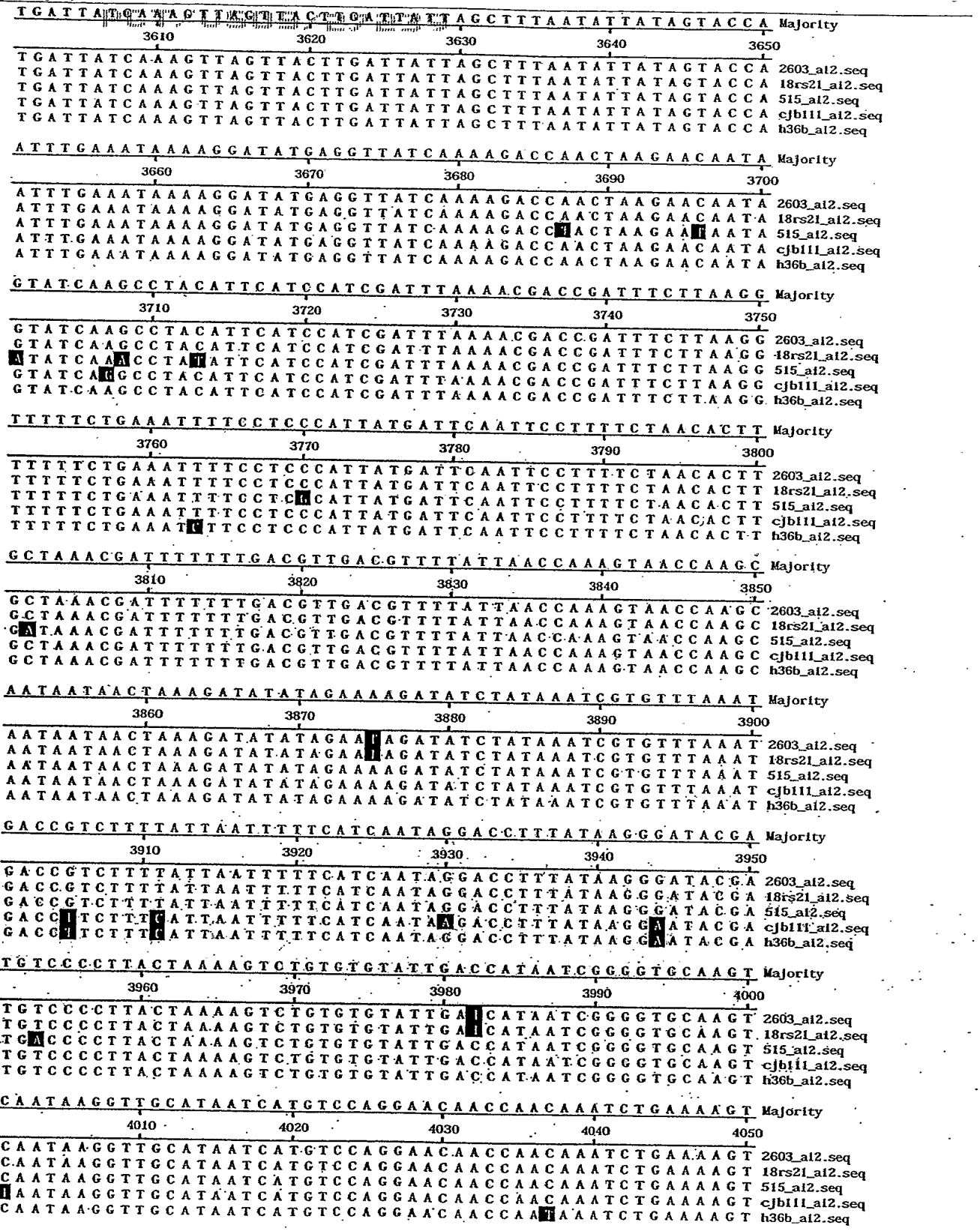
FIGURE 19G


Majority
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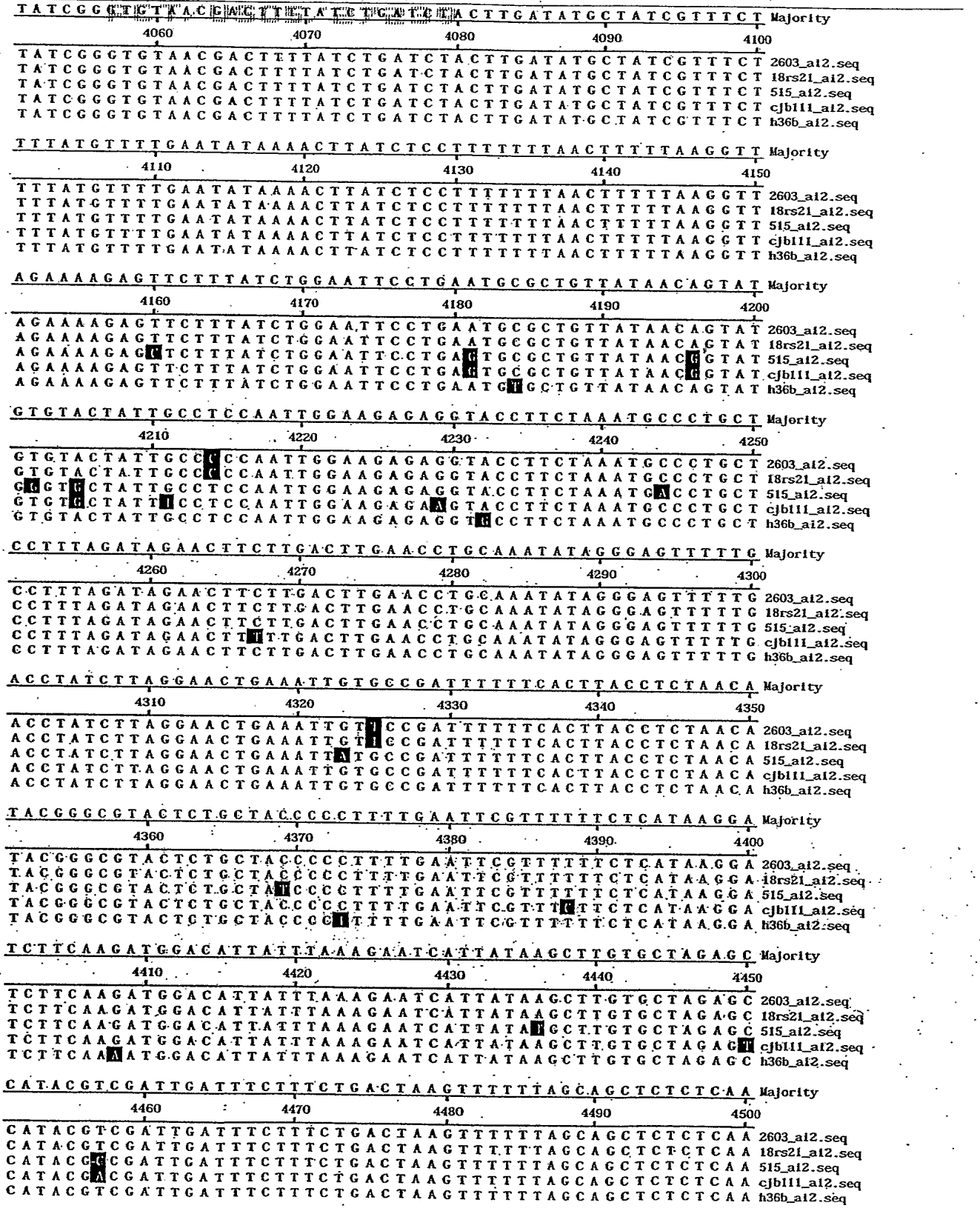
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq

FIGURE 19H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4060 4070 4080 4090 4100
4050 TATCGGGTGTAACGACTTTTATCTGATCTACTTGATATGCTATCGTTTCT 2603_a12.seq
4050 TATCGGGTGTAACGACTTTTATCTGATCTACTTGATATGCTATCGTTTCT 18rs21_a12.seq
4051 TATCGGGTGTAACGACTTTTATCTGATCTACTTGATATGCTATCGTTTCT 515_a12.seq
4050 TATCGGGTGTAACGACTTTTATCTGATCTACTTGATATGCTATCGTTTCT cjb111_a12.seq
4050 TATCGGGTGTAACGACTTTTATCTGATCTACTTGATATGCTATCGTTTCT h36b_a12.seq
TTTATGTTTTGAATATAAAACTTATCTCCTTTTTTTAACTTTTTAAGGTT Majority
4110 4120 4130 4140 4150
4100 TTTATGTTTTGAATATAAAACTTATCTCCTTTTTTTAACTTTTTAAGGTT 2603_a12.seq
4100 TTTATGTTTTGAATATAAAACTTATCTCCTTTTTTTAACTTTTTAAGGTT 18rs21_a12.seq
4101 TTTATGTTTTGAATATAAAACTTATCTCCTTTTTTTAACTTTTTAAGGTT 515_a12.seq
4100 TTTATGTTTTGAATATAAAACTTATCTCCTTTTTTTAACTTTTTAAGGTT cjb111_a12.seq
4100 TTTATGTTTTGAATATAAAACTTATCTCCTTTTTTTAACTTTTTAAGGTT h36b_a12.seq
AGAAAAGAGTTCTTTATCTGGAATTCCTGAATGCGCTGTTATAACAGTAT Majority
4160 4170 4180 4190 4200
4150 AGAAAAGAGTTCTTTATCTGGAATTCCTGAATGCGCTGTTATAACAGTAT 2603_a12.seq
4150 AGAAAAGAGTTCTTTATCTGGAATTCCTGAATGCGCTGTTATAACAGTAT 18rs21_a12.seq
4151 AGAAAAGAGCTCTTTATCTGGAATTCCTGAGTGCGCTGTTATAACGGTAT 515_a12.seq
4150 AGAAAAGAGTTCTTTATCTGGAATTCCTGAGTGCGCTGTTATAACGGTAT cjb111_a12.seq
4150 AGAAAAGAGTTCTTTATCTGGAATTCCTGAATGTGCTGTTATAACAGTAT h36b_a12.seq
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4210 4220 4230 4240 4250
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4200 GTGTACTATTGCCCCCAATTGGAAGAGAGGTACCTTCTAAATGCCCTGCT 18rs21_a12.seq
4201 GCGTGCTATTGCCTCCAATTGGAAGAGAGGTACCTTCTAAATGACCTGCT 515_a12.seq
4200 GTGTGCTATTTCCTCCAATTGGAAGAGAGTACCTTCTAAATGCCCTGCT cjb111_a12.seq
4200 GTGTACTATTGCCTCCAATTGGAAGAGAGGTGCCTTCTAAATGCCCTGCT h36b_a12.seq
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4260 4270 4280 4290 4300
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4250 CCTTTAGATAGAACTTCTTGACTTGAACCTGCAAATATAGGGAGTTTTTG 18rs21_a12.seq
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4250 CCTTTAGATAGAACTTCTTGACTTGAACCTGCAAATATAGGGAGTTTTTG h36b_a12.seq
ACCTATCTTAGGAACTGAAATTGTGCCGATTTTTTCACTTACCTCTAACA Majority
4310 4320 4330 4340 4350
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4301 ACCTATCTTAGGAACTGAAATTATGCCGATTTTTTCACTTACCTCTAACA 515_a12.seq
4300 ACCTATCTTAGGAACTGAAATTGTGCCGATTTTTTCACTTACCTCTAACA cjb111_a12.seq
4300 ACCTATCTTAGGAACTGAAATTGTGCCGATTTTTTCACTTACCTCTAACA h36b_a12.seq
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4360 4370 4380 4390 4400
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TCTTCAAGATGGACATTATTTAAAGAATCATTATAAGCTTGTGCTAGAGC Majority
4410 4420 4430 4440 4450
4400 TCTTCAAGATGGACATTATTTAAAGAATCATTATAAGCTTGTGCTAGAGC 2603_a12.seq
4400 TCTTCAAGATGGACATTATTTAAAGAATCATTATAAGCTTGTGCTAGAGC 18rs21_a12.seq
4401 TCTTCAAGATGGACATTATTTAAAGAATCATTATATGCTTGTGCTAGAGC 515_a12.seq
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CATACGTCGATTGATTTCTTTCTGACTAAGTTTTTTAGCAGCTCTCTCAA Majority
4460 4470 4480 4490 4500
4450 CATACGTCGATTGATTTCTTTCTGACTAAGTTTTTTAGCAGCTCTCTCAA 2603_a12.seq
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FIGURE 191

```
      AATCCTGTGTTTGATTATTAGATTCTATCGTATAGTAAAAACGTGATACC Majority
           4510      4520      4530      4540      4550
4500  AATCCTGTGTTTGATTATTAGATTCTATCGTATAGTAAAAACGTGATACC 2603_ai2.seq
4500  AATCCTGTGTTTGATTATTAGATTCTATCGTATAGTAAAAACGTGATACC 18rs21_ai2.seq
4501  AATCTTGTGTTTGGTTATTAGATTCTATCGTATAGTAAAATCGTGATACC 515_ai2.seq
4500  AATCCTGTGTTTGATTATTAGATTCTATCGTATAGTAAAAACGTGATACC cjb111_ai2.seq
4500  AATCCTGTGTTTGATTATTGGATTCTATCGTATAGTAAAAACGTGATACC h36b_ai2.seq

      ACTGGATACAATAAAATAGATAGACCTATTAGAAAAAGAATGATAAAAGG Majority
           4560      4570      4580      4590      4600
4550  ACTGGATACAATAAAATAGATAGACCTATTAGAAAAAGAATGATAAAAGG 2603_ai2.seq
4550  ACTGGATACAATAAAATAGATAGACCTATTAGAAAAAGAATGATAAAAGG 18rs21_ai2.seq
4551  ACTGGATACAATAAGATAGATAGACCTATTAGAAAAAGAATGATAAAAGG 515_ai2.seq
4550  ACTGGATACAATAAAATAGATAGACCTATTAGAAAAAGAATGATAAAAGG cjb111_ai2.seq
4550  ACTGGATACAATAAAATAGATAGACCTATTAGAAAAAGAATGATAAAAGG h36b_ai2.seq

      AAGATTTGACTTCTTCTTTTT---TGTTTTTTTTGATGATTTTTTTAGTCT Majority
           4610      4620      4630      4640      4650
4600  AAGATTTGACTTCTTCTTTTTTTTTGTTTTTTTTGATGATTTTTTTAGTCT 2603_ai2.seq
4600  AAGATTTGACTTCTTCTTTTTTTTTGTTTTTTTTGATGATTTTTTTAGTCT 18rs21_ai2.seq
4601  GAGATTTGATTTCTTTTTTTT---TGTTTTTTTTGATAATTTTTTTAGTCT 515_ai2.seq
4600  AAGATTTGACTTCTTCTTTTT---AGTTTTTTTTGTTGATATTTTTTAGTCT cjb111_ai2.seq
4600  AAGATTTGACTTCTTCTTTTT---AGTTTTTTTTGATGATATTTTTAGTCT h36b_ai2.seq

      TCACGTCATCTCCTAAATAATGGCTCTTGCTTATGATCTAAGAGTACTTC Majority
           4660      4670      4680      4690      4700
4650  TCACGTCATCTCCTAGATAATGGCTCTTGCTTATGATCTAAGAGTACTTC 2603_ai2.seq
4650  TCACGTCATCTCCTAGATAATGGCTCTTGCTTATGATCTAAGAGTACTTC 18rs21_ai2.seq
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      TACTGAAATACCCTTAGATCATAAGCACAGCTTTAACTGTGCTTATACAT Majority
           4710      4720      4730      4740      4750
4700  TACTGAAATACCCTTAGATCATAAGCACAGCTTTAACTGCGCTTATACAT 2603_ai2.seq
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      CATCAAAGACTAGCCTTAAGCTTCCTCTGATTGACGTCTTTTCATGATAA Majority
           4760      4770      4780      4790      4800
4750  CATCAAAGACTAGCCTTAAGCTTCCTTTGATTGGCGTCTTTTCATGATAA 2603_ai2.seq
4750  CATCAAAGACTAGCCTTAAGCTTCCTTTGATTGGCGTCTTTTCATGATAA 18rs21_ai2.seq
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4747  CATCAAAGACTAGCCTTAAGCTTCCTCTGATTGACGTTTTTTCATGATAA cjb111_ai2.seq
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      CTACTGCTCCAAGCATAATGCTTAAACCAATAATTGTGAAAAGAATTGTA Majority
           4810      4820      4830      4840      4850
4800  CTACTGCTCCAAGCATAATGCTTAAACCAATAATTGTGAAAAGAATTGTA 2603_ai2.seq
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4797  CTACTGCTCCAAGCATAATGCTTAAACCAATAATTGTGAAAAGAATTGTA cjb111_ai2.seq
4797  TTACCGCTCCAAGCATAATGCTTAAACCAATAATTGTGAAAAGAATTGTA h36b_ai2.seq

      CCAATACCACCTGTTTGTGGGATTGTTACCTTTTTATTTTCTACTCGTTG Majority
           4860      4870      4880      4890      4900
4850  CCAATACCACCTGTTTGTGGGATTGTTACCTTTTTATTTTCTACACGTGT 2603_ai2.seq
4850  CCAATACCACCTGTTTGTGGGATTGTTACCTTTTTATTTTCTACACGTGT 18rs21_ai2.seq
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4847  CCAATACCACCTGTTTGTGGGATGGTTACTTTTTTGTTTTGAACTTGTTG cjb111_ai2.seq
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      CGCATCTTTTTTTTTGCTGCTAGCAGCGTAGTCAATGTTACCTG---AAC Majority
           4910      4920      4930      4940      4950
4900  CGCATCTTTTTGGTTGCTGTTAGCAACGTAGTCAATGTTACC------AC 2603_ai2.seq
4900  CGCATCTTTTTGGTTGCTGTTAGCAACGTAGTCAATGTTACC------AC 18rs21_ai2.seq
4898  TGCATCTTTAGTTTTAGAACCTTGGGTATAGTCAATATCTTGAGCAGAAC 515_ai2.seq
4897  GGCATCTTTTTTTACAGAGCCTTTATCATATGCGATGTCAGTTGTAGCTC cjb111_ai2.seq
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FIGURE 19J

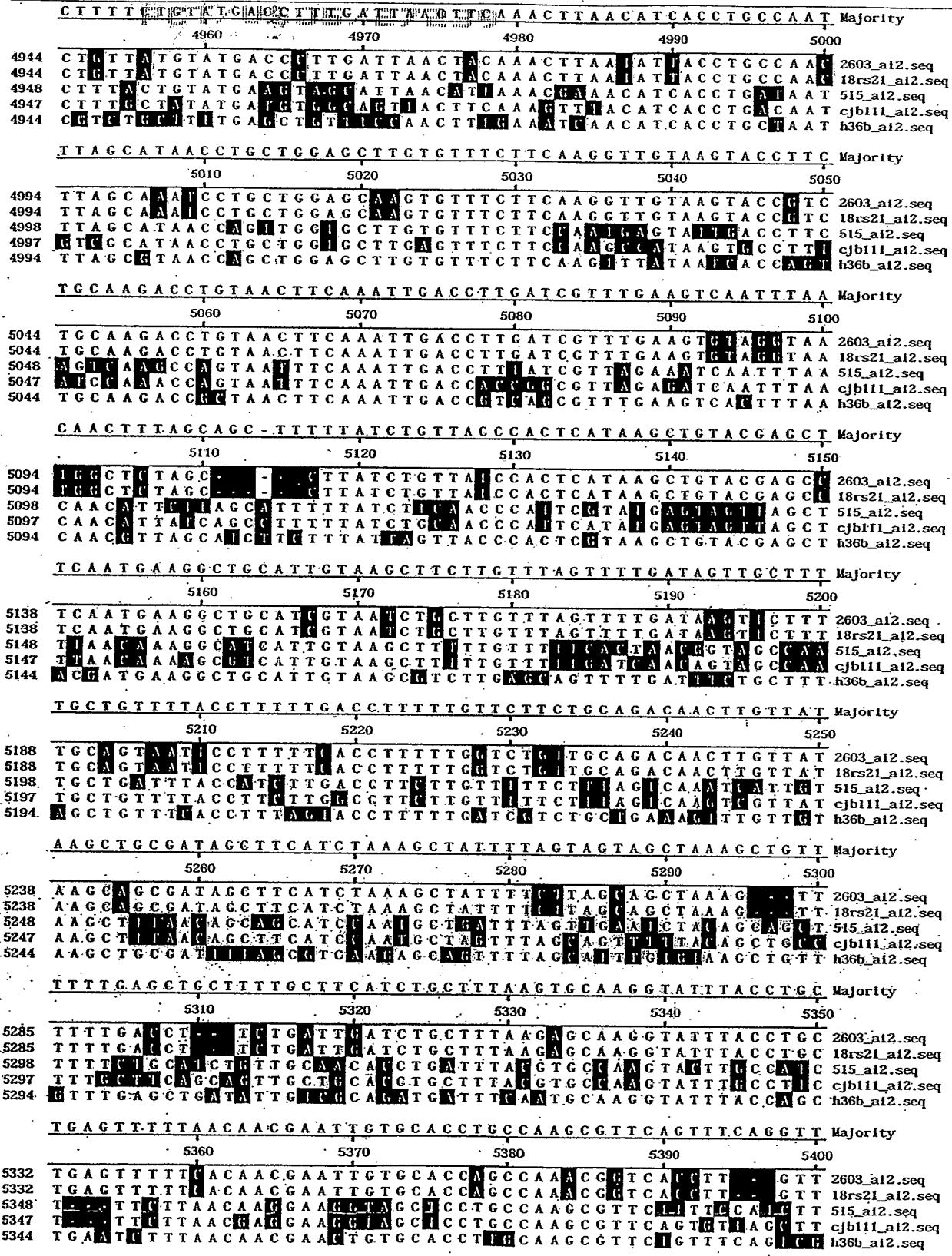
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FIGURE 19K

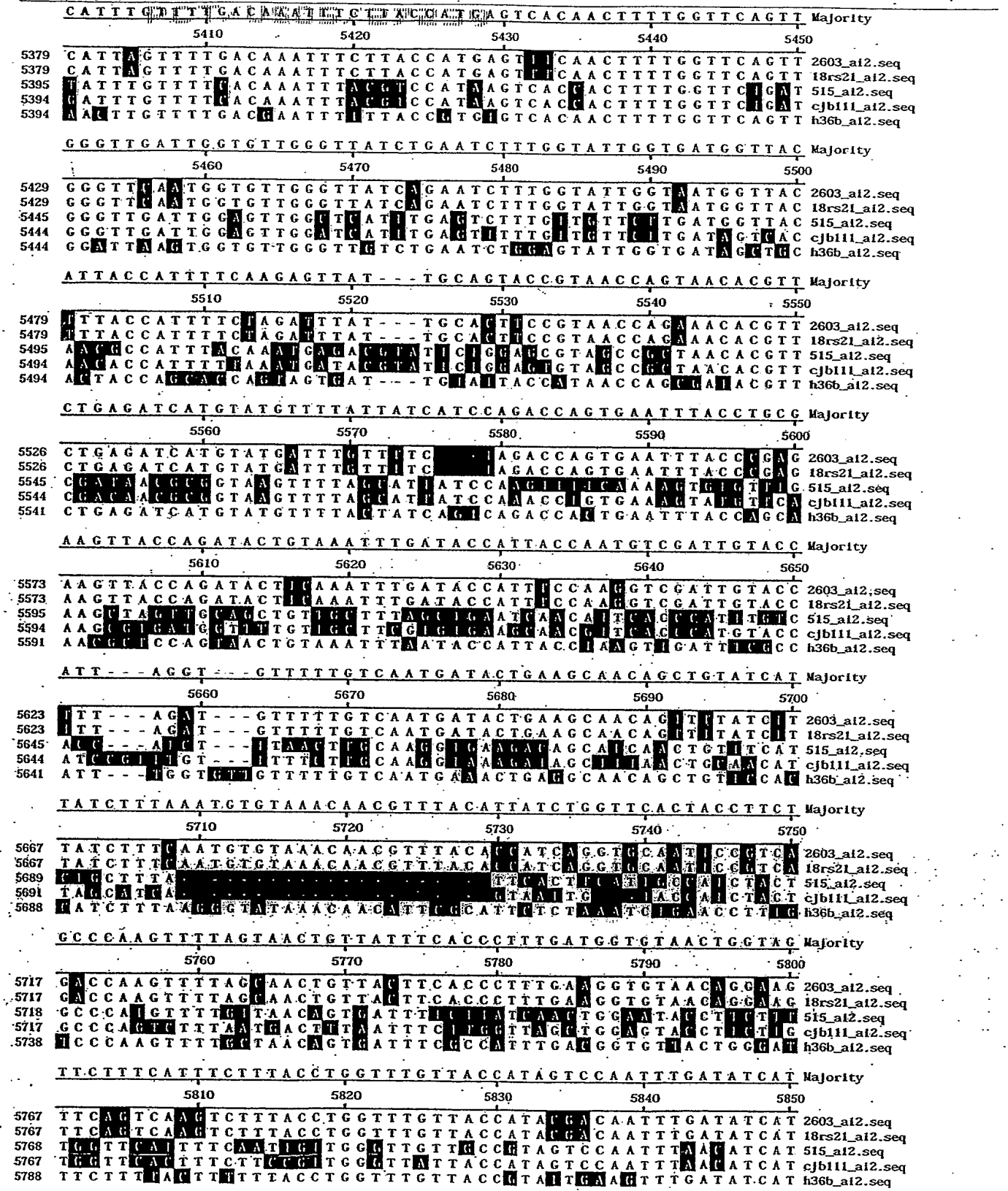
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FIGURE 19L

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FIGURE 19M

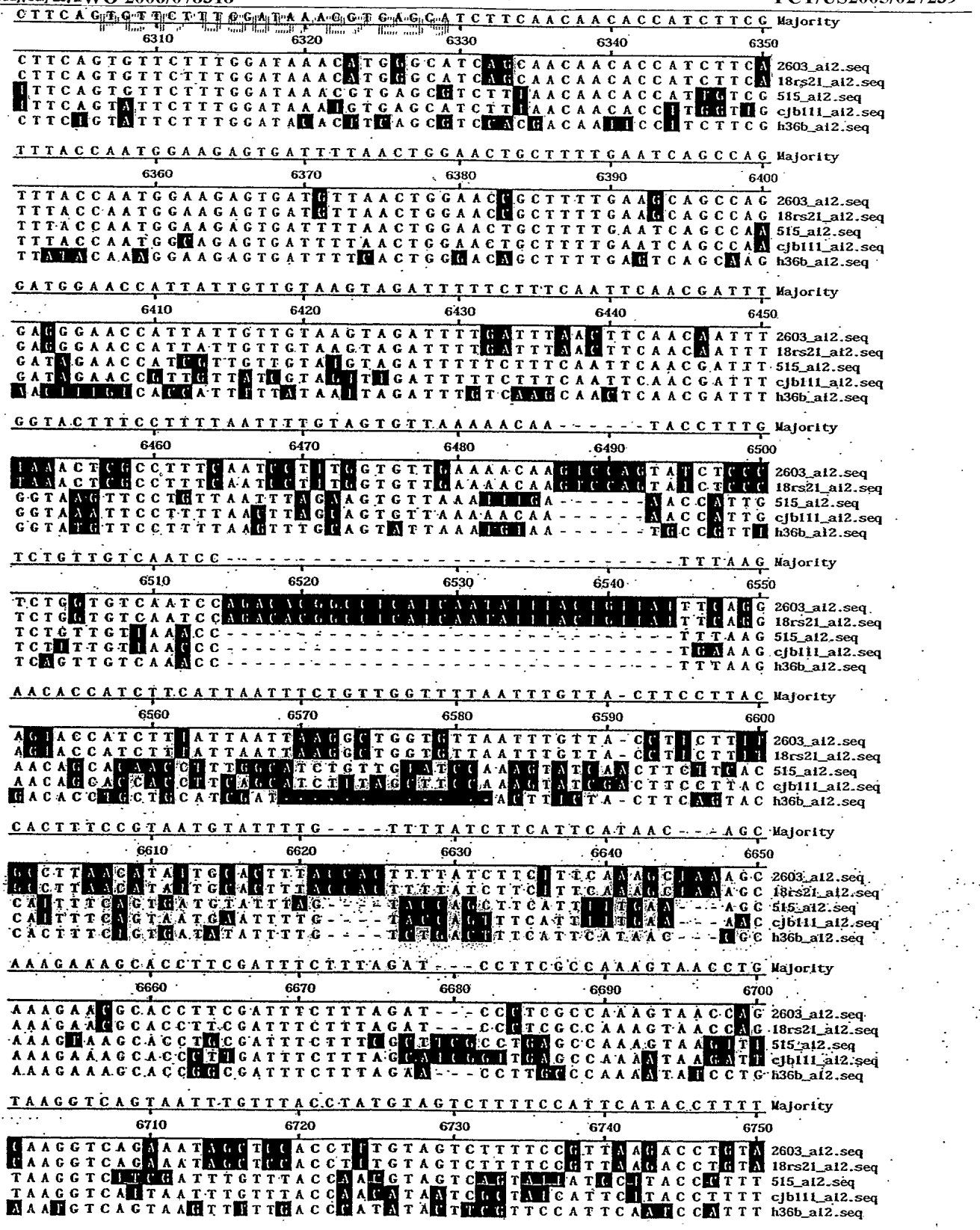
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FIGURE 19N

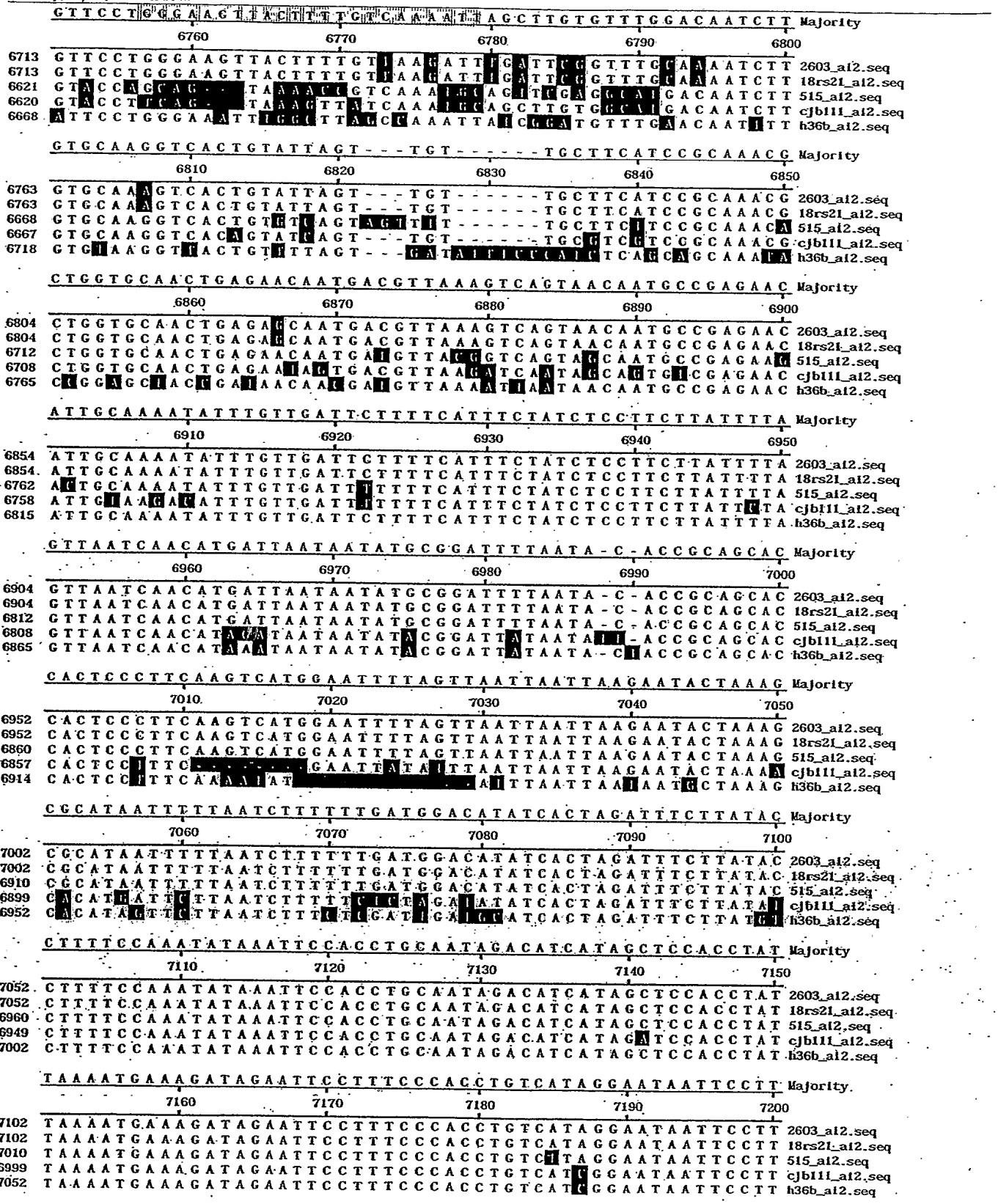
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FIGURE 19O

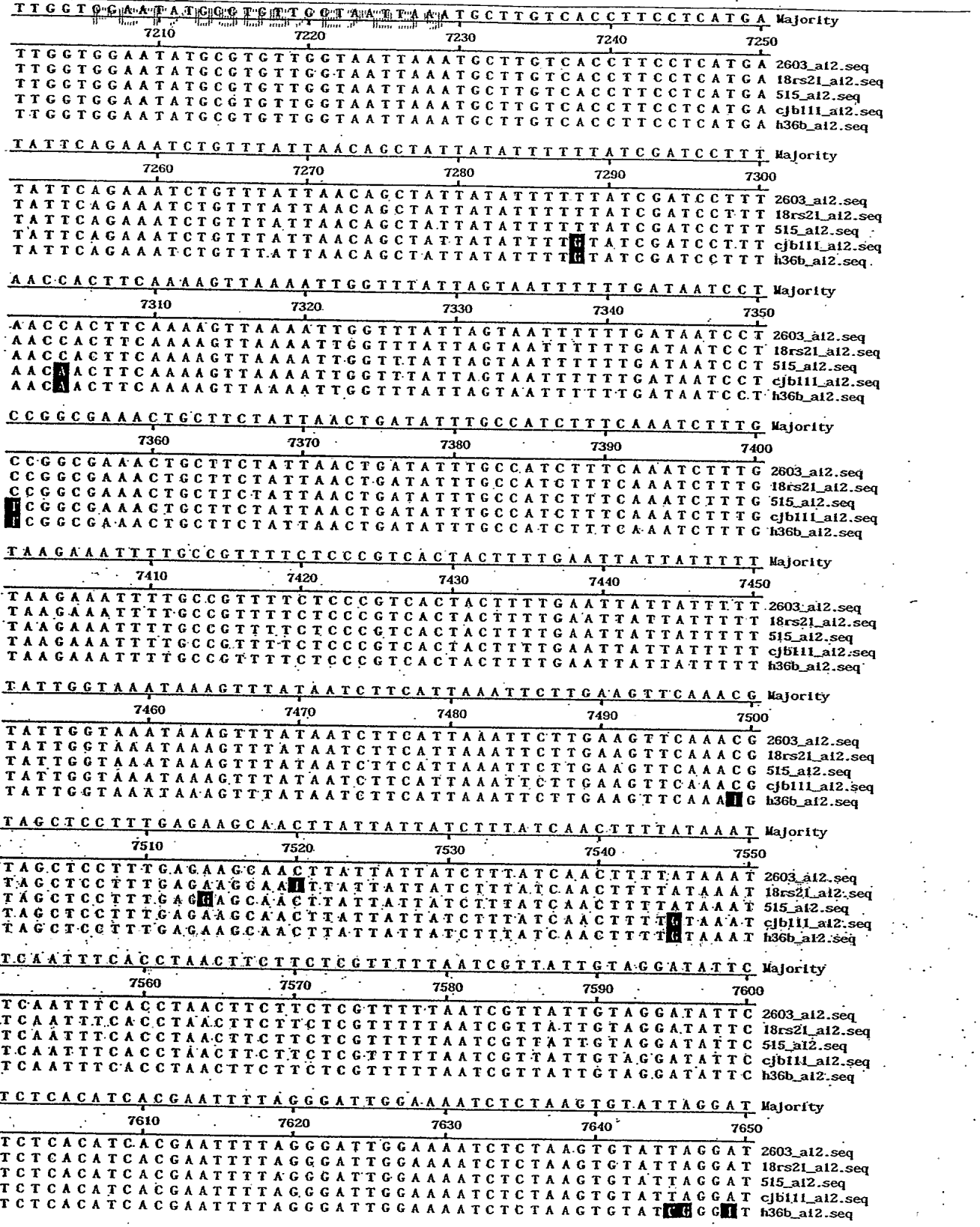
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FIGURE 19P

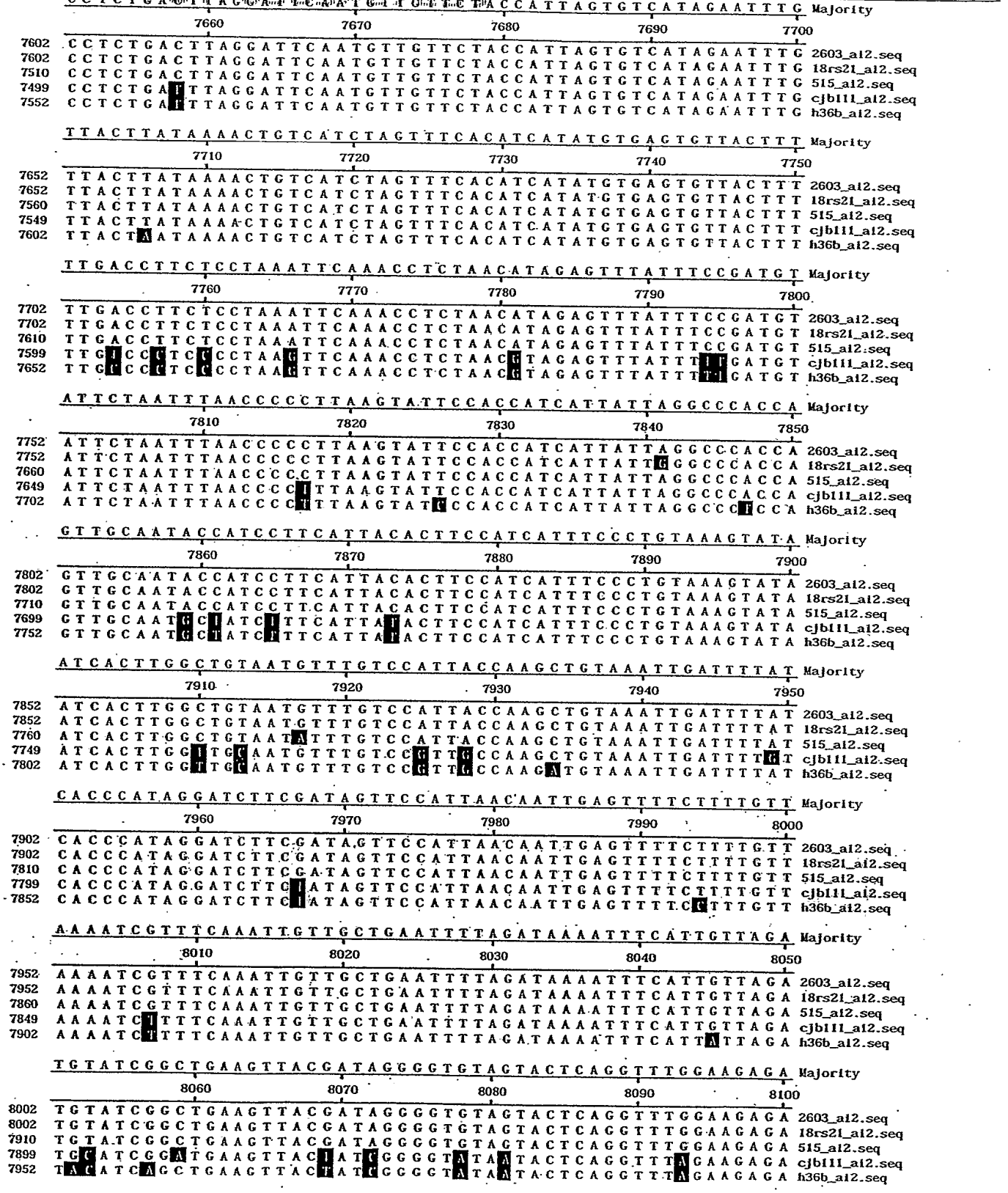
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FIGURE 19Q

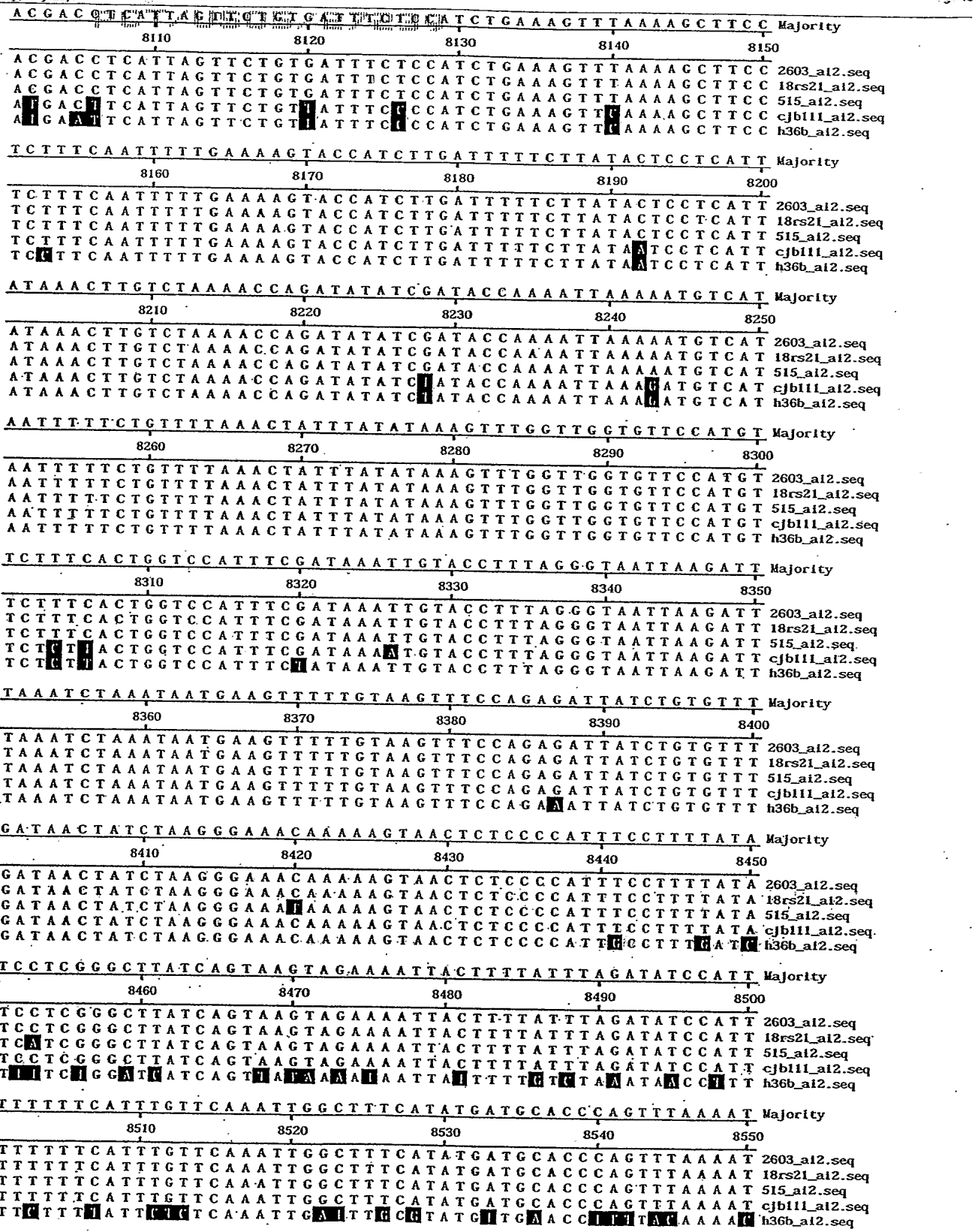
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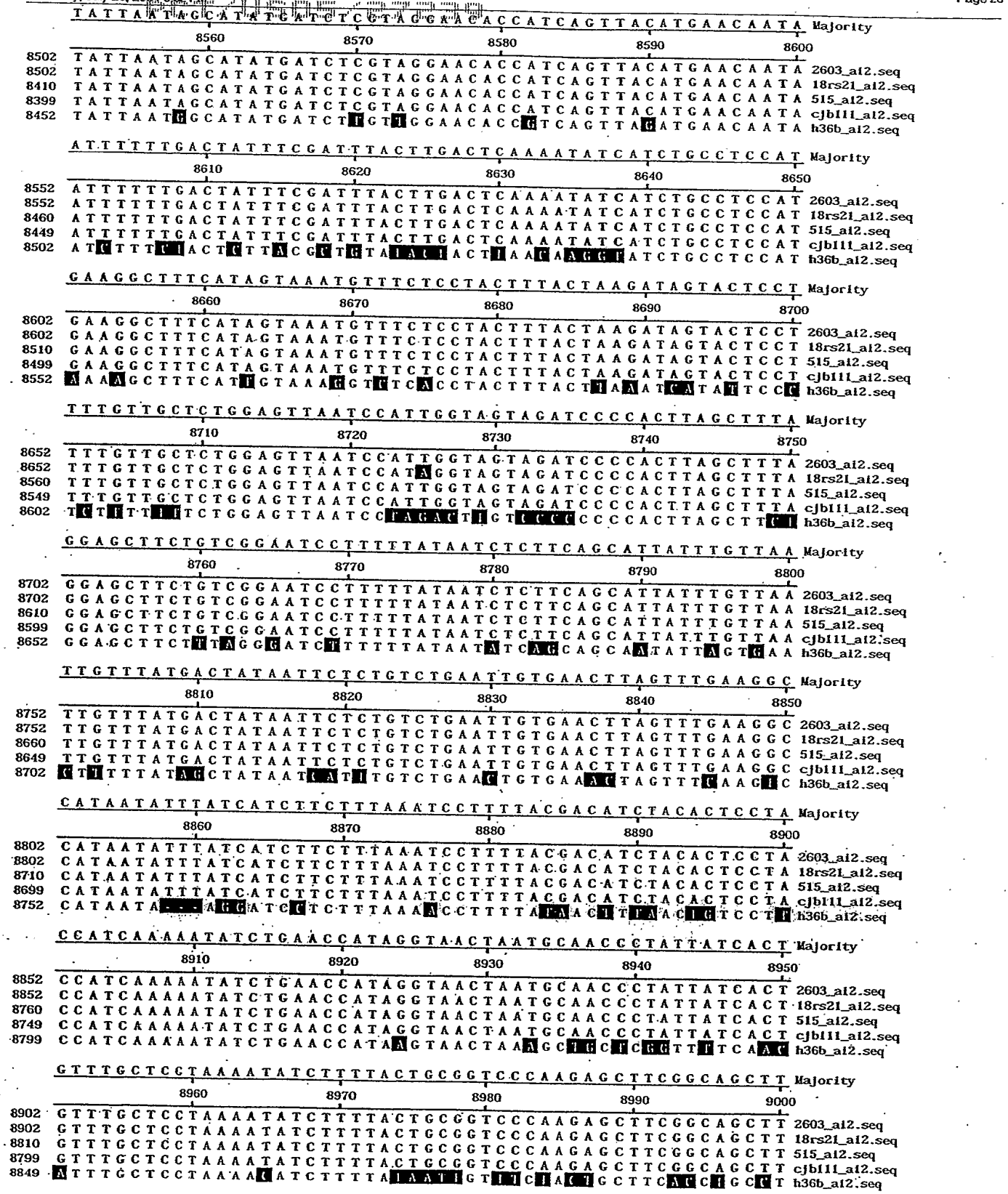
FIGURE 19R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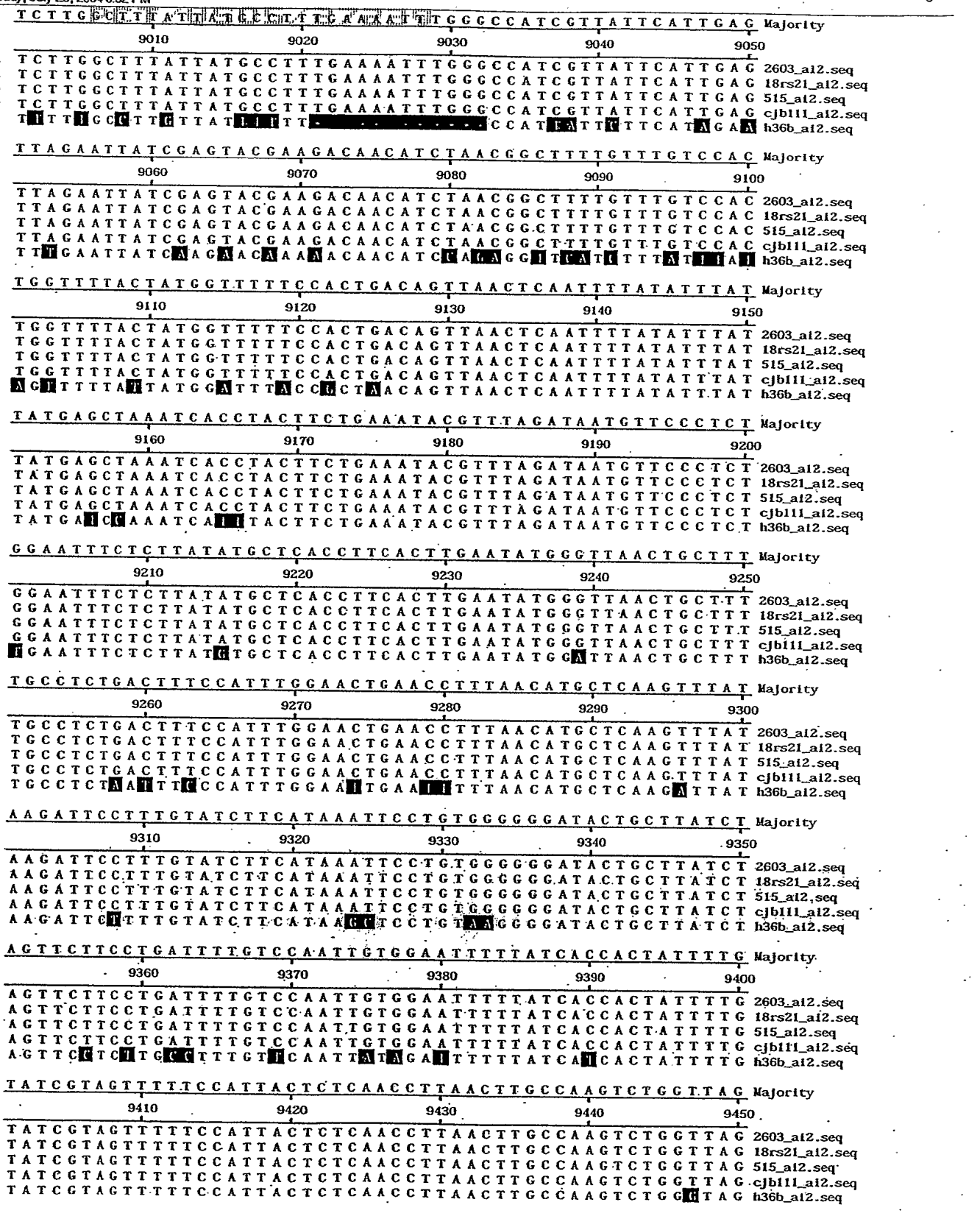
8702 GGAGCTTCTGTCGGAATCCTTTTTATAATCTCTTCAGCATTATTTGTTAA 2603_al2.seq
8702 GGAGCTTCTGTCGGAATCCTTTTTATAATCTCTTCAGCATTATTTGTTAA 18rs21_al2.seq
8610 GGAGCTTCTGTCGGAATCCTTTTTATAATCTCTTCAGCATTATTTGTTAA 515_al2.seq
8599 GGAGCTTCTGTCGGAATCCTTTTTATAATCTCTTCAGCATTATTTGTTAA cjb111_al2.seq
8652 GGAGCTTCTTTTAGGGATCTTTTTTATAATATCAGCAGCAATATTAGTGAA h36b_al2.seq
TTGTTTATGACTATAATTCTCTGTCTGAATTGTGAACTTAGTTTGAAGGC Majority
8810 8820 8830 8840 8850
8752 TTGTTTATGACTATAATTCTCTGTCTGAATTGTGAACTTAGTTTGAAGGC 2603_al2.seq
8752 TTGTTTATGACTATAATTCTCTGTCTGAATTGTGAACTTAGTTTGAAGGC 18rs21_al2.seq
8660 TTGTTTATGACTATAATTCTCTGTCTGAATTGTGAACTTAGTTTGAAGGC 515_al2.seq
8649 TTGTTTATGACTATAATTCTCTGTCTGAATTGTGAACTTAGTTTGAAGGC cjb111_al2.seq
8702 CTTTTTATAGCTATAATCATTGTCTGAACTGTGAAACTAGTTTGAAGTC h36b_al2.seq
CATAATATTTATCATCTTCTTTAAATCCTTTTACGACATCTACACTCCTA Majority
8860 8870 8880 8890 8900
8802 CATAATATTTATCATCTTCTTTAAATCCTTTTACGACATCTACACTCCTA 2603_al2.seq
8802 CATAATATTTATCATCTTCTTTAAATCCTTTTACGACATCTACACTCCTA 18rs21_al2.seq
8710 CATAATATTTATCATCTTCTTTAAATCCTTTTACGACATCTACACTCCTA 515_al2.seq
8699 CATAATATTTATCATCTTCTTTAAATCCTTTTACGACATCTACACTCCTA cjb111_al2.seq
8752 CATAATA---AGGATCCTCTTTAAAACCTTTTAAACTTAACTGTCCTT h36b_al2.seq
CCATCAAAAATATCTGAACCATAGGTAACTAATGCAACCCTATTATCACT Majority
8910 8920 8930 8940 8950
8852 CCATCAAAAATATCTGAACCATAGGTAACTAATGCAACCCTATTATCACT 2603_al2.seq
8852 CCATCAAAAATATCTGAACCATAGGTAACTAATGCAACCCTATTATCACT 18rs21_al2.seq
8760 CCATCAAAAATATCTGAACCATAGGTAACTAATGCAACCCTATTATCACT 515_al2.seq
8749 CCATCAAAAATATCTGAACCATAGGTAACTAATGCAACCCTATTATCACT cjb111_al2.seq
8799 CCATCAAAAATATCTGAACCATAAGTAACTAAAGCTGCTCGGTTTCAAG h36b_al2.seq
GTTTGCTCCTAAAATATCTTTTACTGCGGTCCCAAGAGCTTCGGCAGCTT Majority
8960 8970 8980 8990 9000
8902 GTTTGCTCCTAAAATATCTTTTACTGCGGTCCCAAGAGCTTCGGCAGCTT 2603_al2.seq
8902 GTTTGCTCCTAAAATATCTTTTACTGCGGTCCCAAGAGCTTCGGCAGCTT 18rs21_al2.seq
8810 GTTTGCTCCTAAAATATCTTTTACTGCGGTCCCAAGAGCTTCGGCAGCTT 515_al2.seq
8799 GTTTGCTCCTAAAATATCTTTTACTGCGGTCCCAAGAGCTTCGGCAGCTT cjb111_al2.seq
8849 ATTTGCTCCTAAAACATCTTTTAIAATIGTTTCIACTGCTTCACCIGCCT h36b_al2.seq

FIGURE 19S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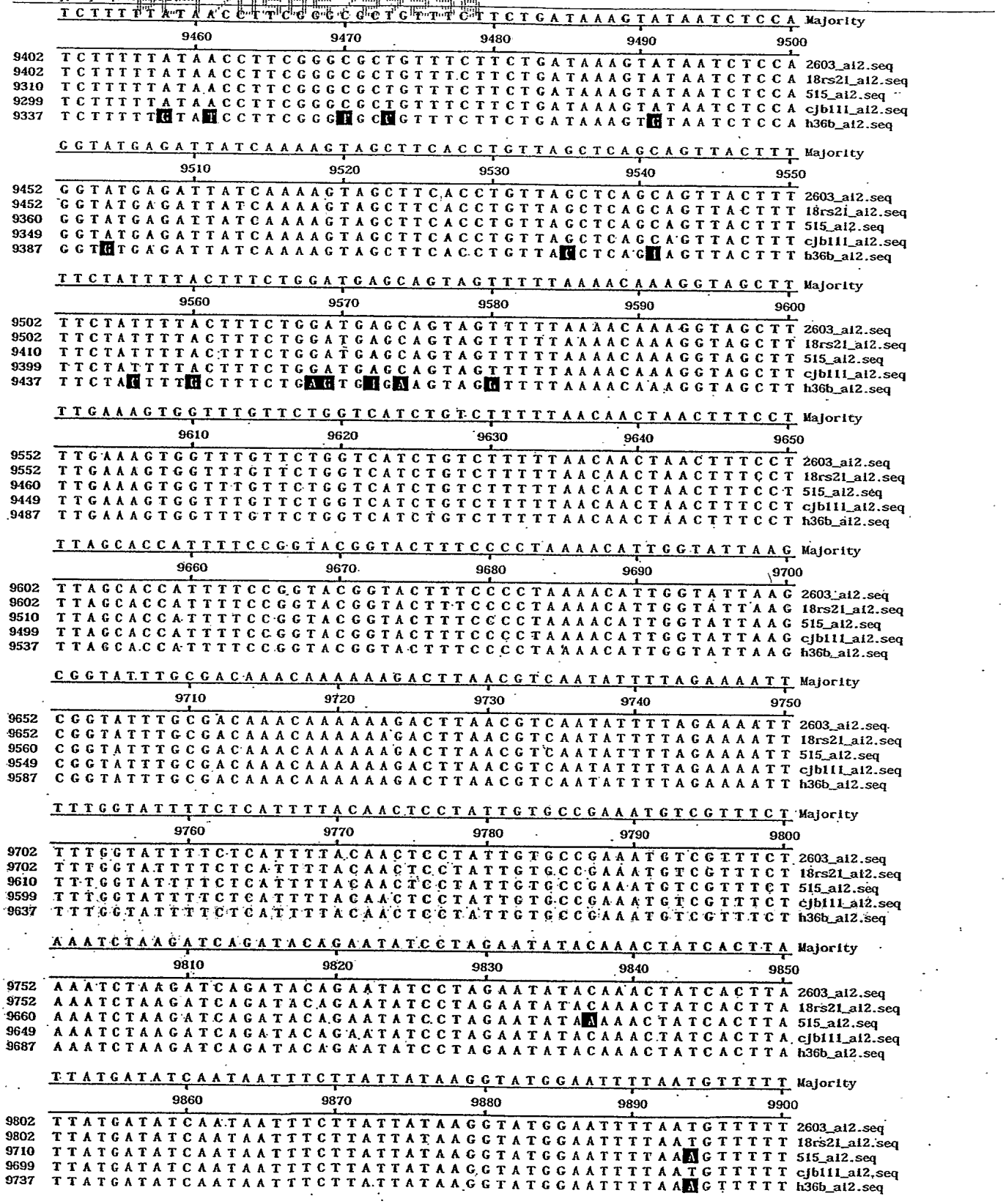
9010 9020 9030 9040 9050
9060 9070 9080 9090 9100
9110 9120 9130 9140 9150
9160 9170 9180 9190 9200
9210 9220 9230 9240 9250
9260 9270 9280 9290 9300
9310 9320 9330 9340 9350
9360 9370 9380 9390 9400
9410 9420 9430 9440 9450
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq

FIGURE 19T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9402 TCTTTTTATAACCTTCGGGCCGCTGTTTCTTCTGATAAAGTATAATCTCCA 2603_a12.seq
9402 TCTTTTTATAACCTTCGGGCCGCTGTTTCTTCTGATAAAGTATAATCTCCA 18rs21_a12.seq
9310 TCTTTTTATAACCTTCGGGCCGCTGTTTCTTCTGATAAAGTATAATCTCCA 515_a12.seq
9299 TCTTTTTATAACCTTCGGGCCGCTGTTTCTTCTGATAAAGTATAATCTCCA cjb111_a12.seq
9337 TCTTTTTGTATCCTTCGGGTGCGTTTCTTCTGATAAAGTGTAATCTCCA h36b_a12.seq
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9510 9520 9530 9540 9550
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9452 GGTATGAGATTATCAAAAGTAGCTTCACCTGTTAGCTCAGCAGTTACTTT 18rs21_a12.seq
9360 GGTATGAGATTATCAAAAGTAGCTTCACCTGTTAGCTCAGCAGTTACTTT 515_a12.seq
9349 GGTATGAGATTATCAAAAGTAGCTTCACCTGTTAGCTCAGCAGTTACTTT cjb111_a12.seq
9387 GGTGTGAGATTATCAAAAGTAGCTTCACCTGTTACCTCAGTAGTTACTTT h36b_a12.seq
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9560 9570 9580 9590 9600
9502 TTCTATTTTACTTTCTGGATGAGCAGTAGTTTTTAAAACAAAGGTAGCTT 2603_a12.seq
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9410 TTCTATTTTACTTTCTGGATGAGCAGTAGTTTTTAAAACAAAGGTAGCTT 515_a12.seq
9399 TTCTATTTTACTTTCTGGATGAGCAGTAGTTTTTAAAACAAAGGTAGCTT cjb111_a12.seq
9437 TTCTACTTTTGCTTTCTGAGTGTGAAGTAGGTTTTTAAAACAAAGGTAGCTT h36b_a12.seq
TTGAAAGTGGTTTGTTCTGGTCATCTGTCTTTTTAACAACTAACTTTCCT Majority
9610 9620 9630 9640 9650
9552 TTGAAAGTGGTTTGTTCTGGTCATCTGTCTTTTTAACAACTAACTTTCCT 2603_a12.seq
9552 TTGAAAGTGGTTTGTTCTGGTCATCTGTCTTTTTAACAACTAACTTTCCT 18rs21_a12.seq
9460 TTGAAAGTGGTTTGTTCTGGTCATCTGTCTTTTTAACAACTAACTTTCCT 515_a12.seq
9449 TTGAAAGTGGTTTGTTCTGGTCATCTGTCTTTTTAACAACTAACTTTCCT cjb111_a12.seq
9487 TTGAAAGTGGTTTGTTCTGGTCATCTGTCTTTTTAACAACTAACTTTCCT h36b_a12.seq
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9660 9670 9680 9690 9700
9602 TTAGCACCATTTTCCGGTACGGTACTTTCCCCTAAAACATTGGTATTAAG 2603_a12.seq
9602 TTAGCACCATTTTCCGGTACGGTACTTTCCCCTAAAACATTGGTATTAAG 18rs21_a12.seq
9510 TTAGCACCATTTTCCGGTACGGTACTTTCCCCTAAAACATTGGTATTAAG 515_a12.seq
9499 TTAGCACCATTTTCCGGTACGGTACTTTCCCCTAAAACATTGGTATTAAG cjb111_a12.seq
9537 TTAGCACCATTTTCCGGTACGGTACTTTCCCCTAAAACATTGGTATTAAG h36b_a12.seq
CGGTATTTGCGACAAACAAAAAAGACTTAACGTCAATATTTTAGAAAATT Majority
9710 9720 9730 9740 9750
9652 CGGTATTTGCGACAAACAAAAAAGACTTAACGTCAATATTTTAGAAAATT 2603_a12.seq
9652 CGGTATTTGCGACAAACAAAAAAGACTTAACGTCAATATTTTAGAAAATT 18rs21_a12.seq
9560 CGGTATTTGCGACAAACAAAAAAGACTTAACGTCAATATTTTAGAAAATT 515_a12.seq
9549 CGGTATTTGCGACAAACAAAAAAGACTTAACGTCAATATTTTAGAAAATT cjb111_a12.seq
9587 CGGTATTTGCGACAAACAAAAAAGACTTAACGTCAATATTTTAGAAAATT h36b_a12.seq
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9760 9770 9780 9790 9800
9702 TTTGGTATTTTCTCATTTTACAACTCCTATTGTGCCGAAATGTCGTTTCT 2603_a12.seq
9702 TTTGGTATTTTCTCATTTTACAACTCCTATTGTGCCGAAATGTCGTTTCT 18rs21_a12.seq
9610 TTTGGTATTTTCTCATTTTACAACTCCTATTGTGCCGAAATGTCGTTTCT 515_a12.seq
9599 TTTGGTATTTTCTCATTTTACAACTCCTATTGTGCCGAAATGTCGTTTCT cjb111_a12.seq
9637 TTTGGTATTTTCTCATTTTACAACTCCTATTGTGCCGAAATGTCGTTTCT h36b_a12.seq
AAATCTAAGATCAGATACAGAATATCCTAGAATATACAAACTATCACTTA Majority
9810 9820 9830 9840 9850
9752 AAATCTAAGATCAGATACAGAATATCCTAGAATATACAAACTATCACTTA 2603_a12.seq
9752 AAATCTAAGATCAGATACAGAATATCCTAGAATATACAAACTATCACTTA 18rs21_a12.seq
9660 AAATCTAAGATCAGATACAGAATATCCTAGAATATAAAACTATCACTTA 515_a12.seq
9649 AAATCTAAGATCAGATACAGAATATCCTAGAATATACAAACTATCACTTA cjb111_a12.seq
9687 AAATCTAAGATCAGATACAGAATATCCTAGAATATACAAACTATCACTTA h36b_a12.seq
TTATGATATCAATAATTTCTTATTATAAGGTATGGAATTTTAATGTTTTT Majority
9860 9870 9880 9890 9900
9802 TTATGATATCAATAATTTCTTATTATAAGGTATGGAATTTTAATGTTTTT 2603_a12.seq
9802 TTATGATATCAATAATTTCTTATTATAAGGTATGGAATTTTAATGTTTTT 18rs21_a12.seq
9710 TTATGATATCAATAATTTCTTATTATAAGGTATGGAATTTTAAAGTTTTT 515_a12.seq
9699 TTATGATATCAATAATTTCTTATTATAAGGTATGGAATTTTAATGTTTTT cjb111_a12.seq
9737 TTATGATATCAATAATTTCTTATTATAAGGTATGGAATTTTAAAGTTTTT h36b_a12.seq

FIGURE 19U

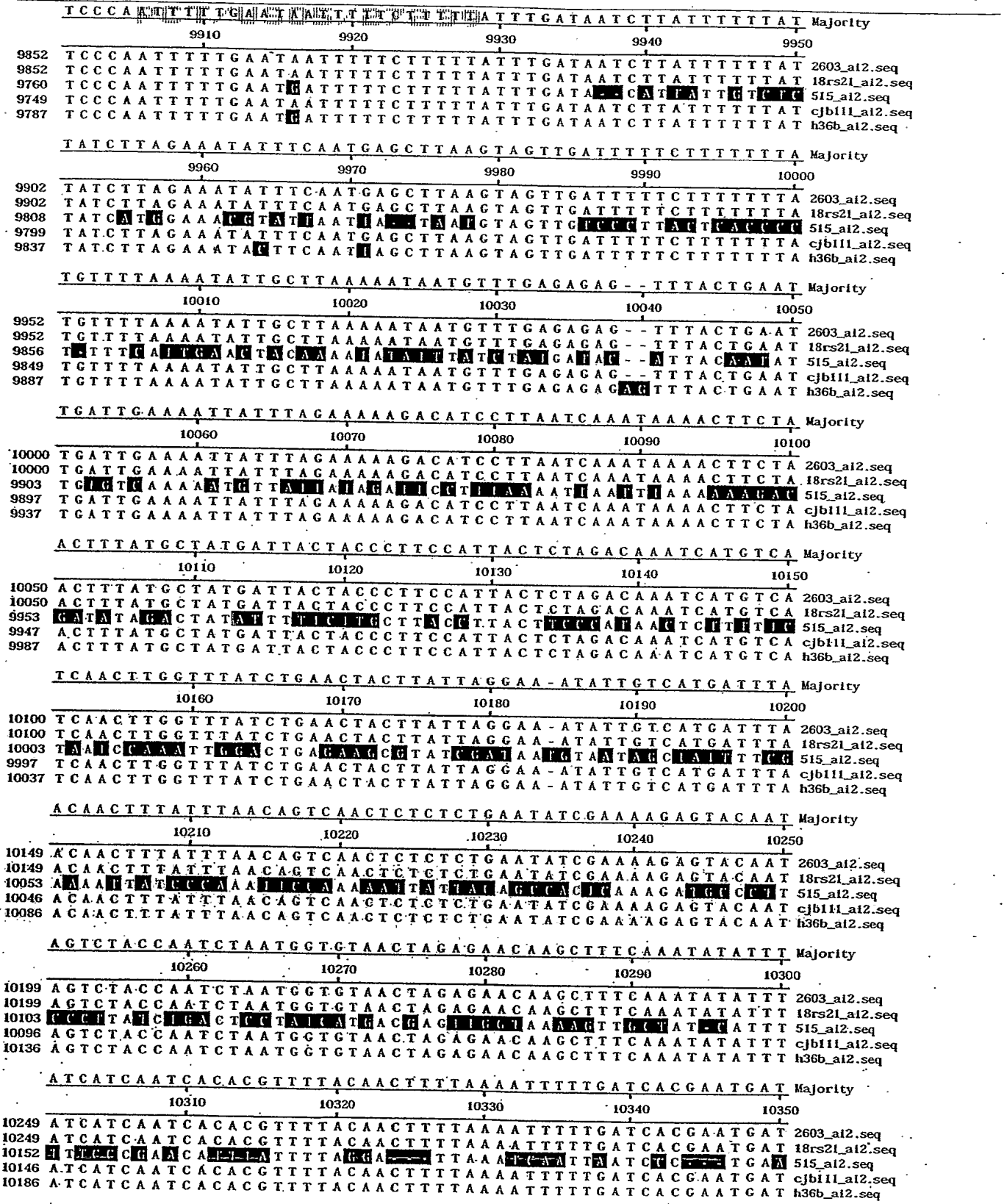

Majority
2603_al2.seq
18rs21_al2.seq
515_al2.seq
cjb111_al2.seq
h36b_al2.seq

FIGURE 19V

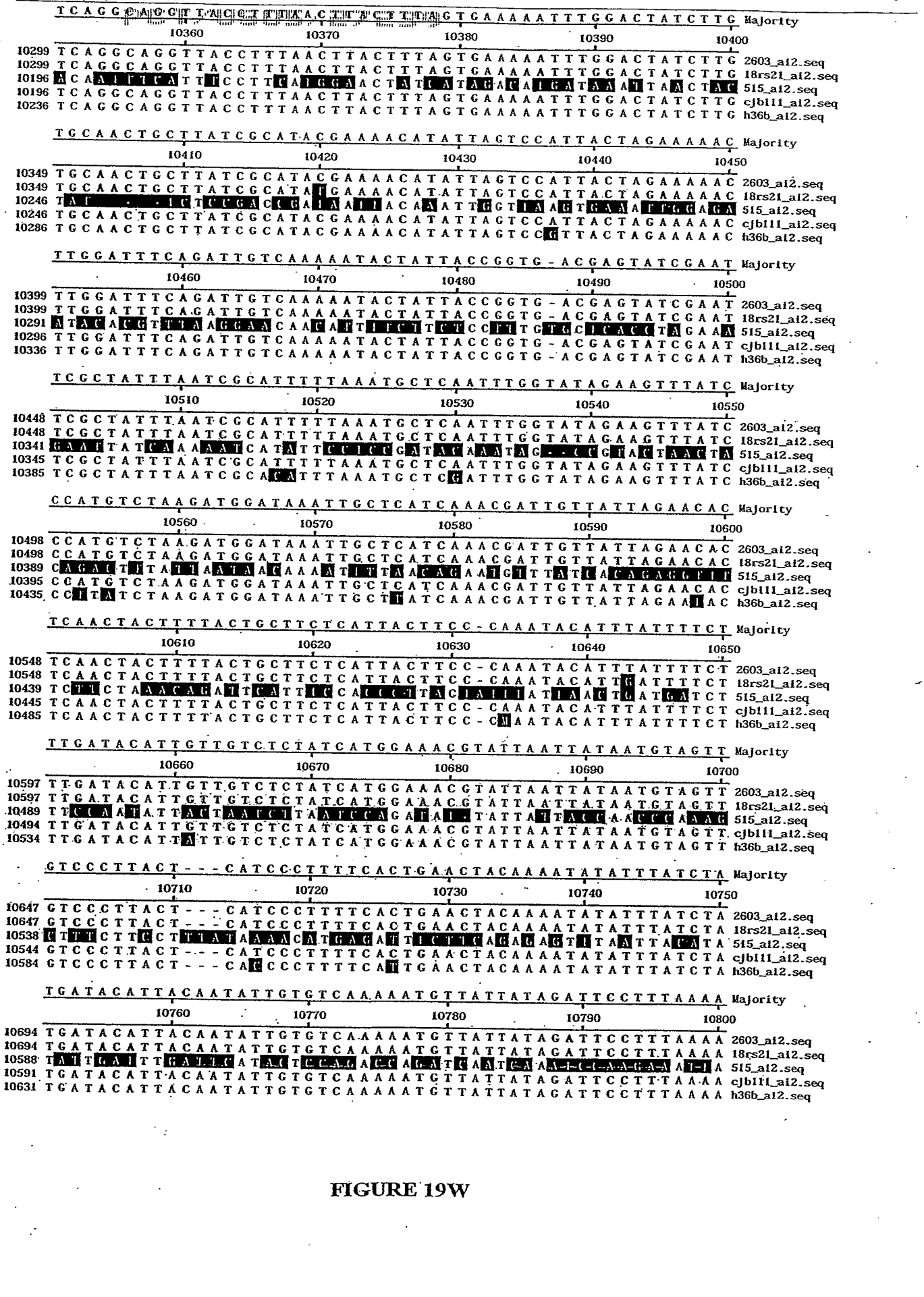

Majority
10360 10370 10380 10390 10400
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
Majority
10410 10420 10430 10440 10450
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
Majority
10460 10470 10480 10490 10500
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
Majority
10510 10520 10530 10540 10550
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
Majority
10560 10570 10580 10590 10600
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
Majority
10610 10620 10630 10640 10650
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
Majority
10660 10670 10680 10690 10700
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
Majority
10710 10720 10730 10740 10750
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
Majority
10760 10770 10780 10790 10800
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq

FIGURE 19W

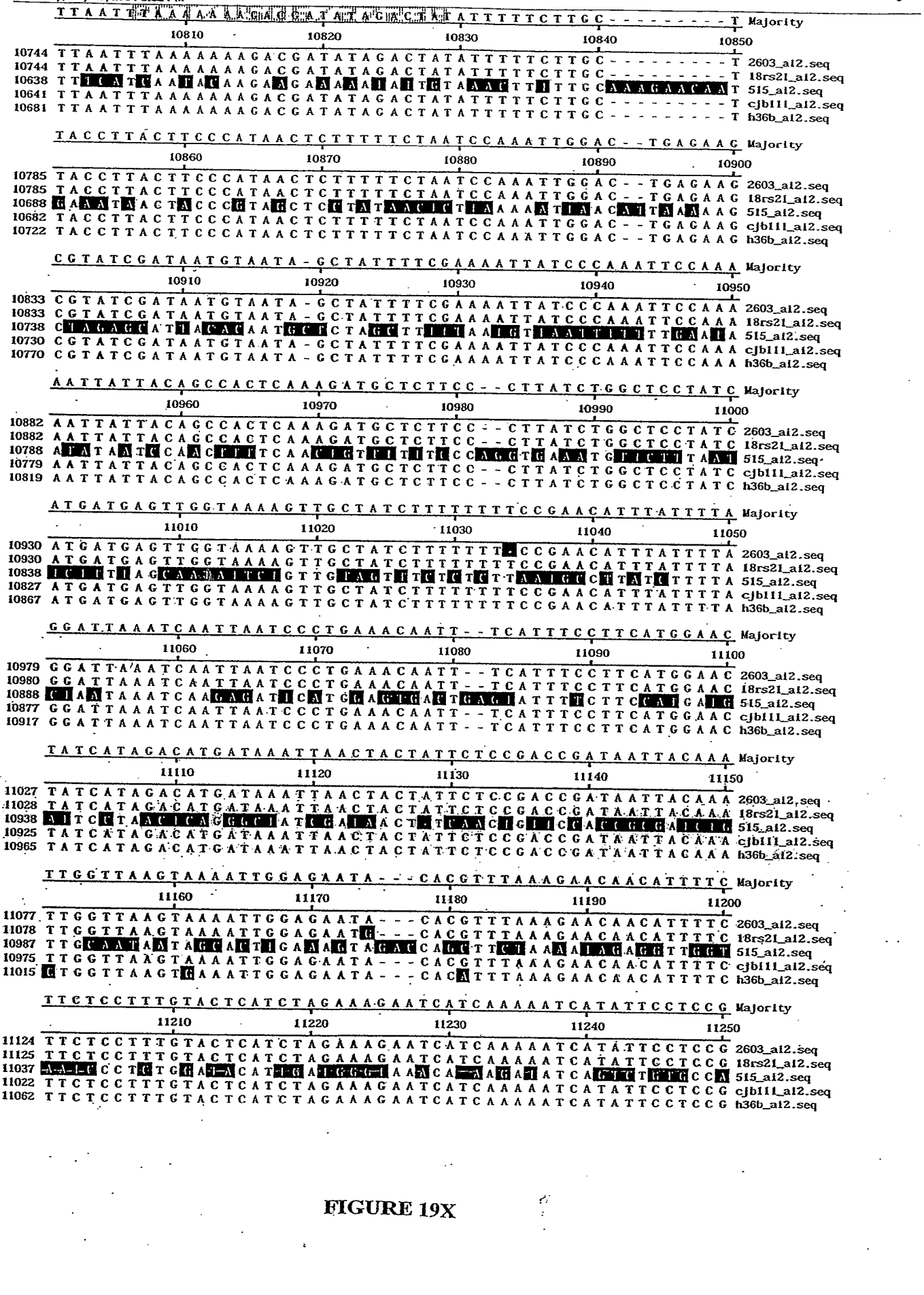

Majority
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq

FIGURE 19X

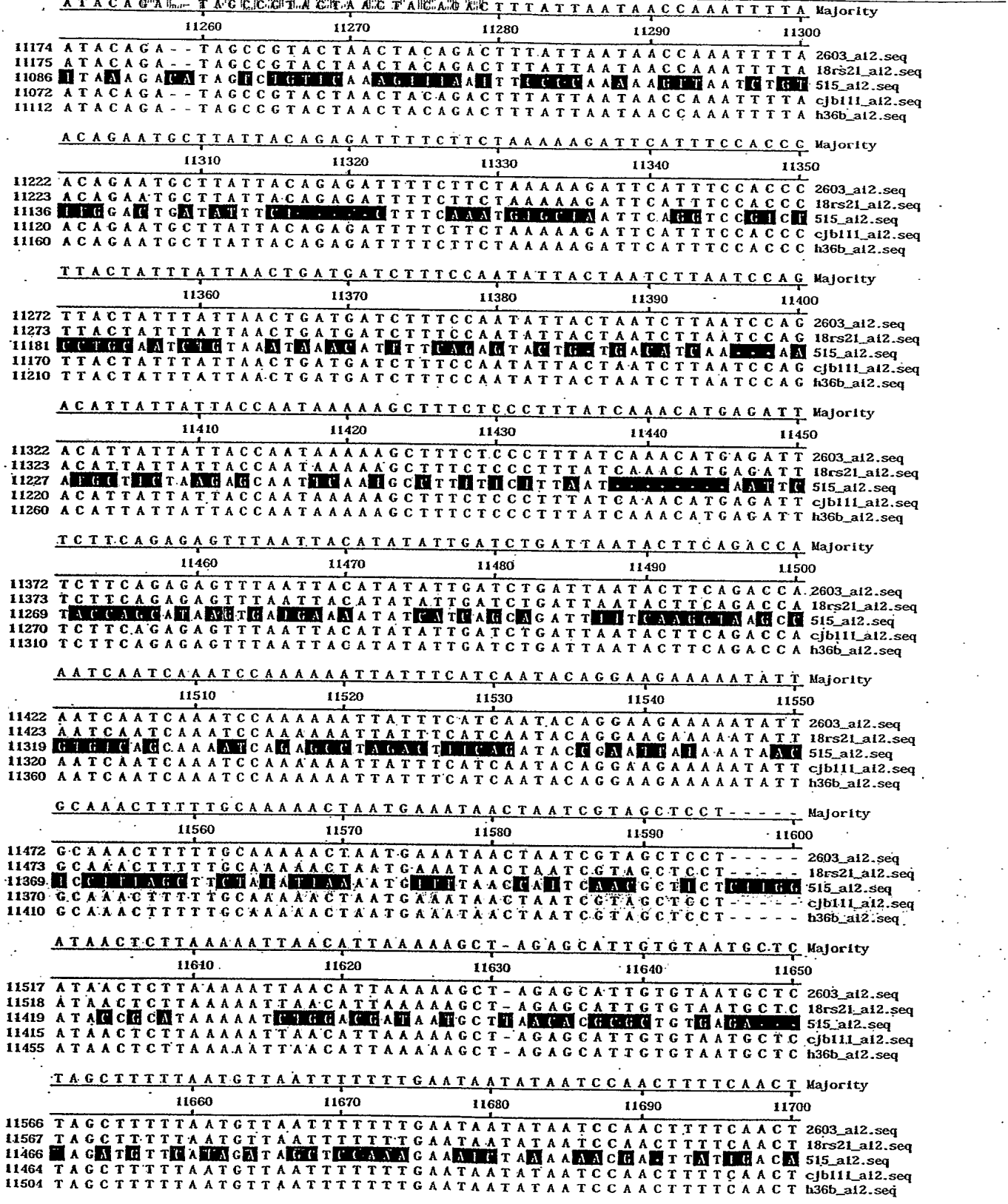
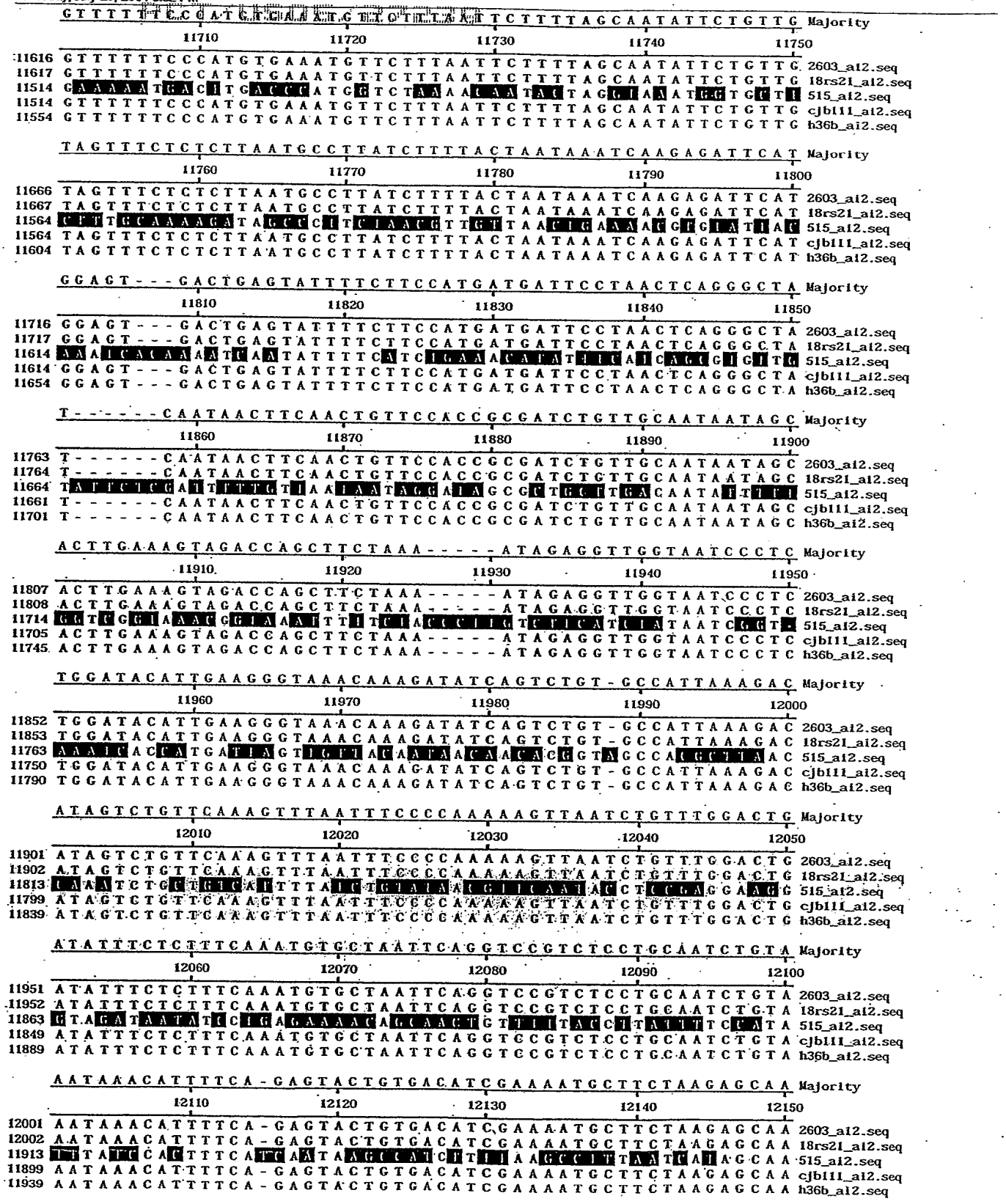

Majority
11260 11270 11280 11290 11300
11174 2603_a12.seq
11175 18rs21_a12.seq
11086 515_a12.seq
11072 cjb111_a12.seq
11112 h36b_a12.seq
Majority
11310 11320 11330 11340 11350
11222 2603_a12.seq
11223 18rs21_a12.seq
11136 515_a12.seq
11120 cjb111_a12.seq
11160 h36b_a12.seq
Majority
11360 11370 11380 11390 11400
11272 2603_a12.seq
11273 18rs21_a12.seq
11181 515_a12.seq
11170 cjb111_a12.seq
11210 h36b_a12.seq
Majority
11410 11420 11430 11440 11450
11322 2603_a12.seq
11323 18rs21_a12.seq
11227 515_a12.seq
11220 cjb111_a12.seq
11260 h36b_a12.seq
Majority
11460 11470 11480 11490 11500
11372 2603_a12.seq
11373 18rs21_a12.seq
11269 515_a12.seq
11270 cjb111_a12.seq
11310 h36b_a12.seq
Majority
11510 11520 11530 11540 11550
11422 2603_a12.seq
11423 18rs21_a12.seq
11319 515_a12.seq
11320 cjb111_a12.seq
11360 h36b_a12.seq
Majority
11560 11570 11580 11590 11600
11472 2603_a12.seq
11473 18rs21_a12.seq
11369 515_a12.seq
11370 cjb111_a12.seq
11410 h36b_a12.seq
Majority
11610 11620 11630 11640 11650
11517 2603_a12.seq
11518 18rs21_a12.seq
11419 515_a12.seq
11415 cjb111_a12.seq
11455 h36b_a12.seq
Majority
11660 11670 11680 11690 11700
11566 2603_a12.seq
11567 18rs21_a12.seq
11466 515_a12.seq
11464 cjb111_a12.seq
11504 h36b_a12.seq

FIGURE 19Y


Majority
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11760 11770 11780 11790 11800
11810 11820 11830 11840 11850
11860 11870 11880 11890 11900
11910 11920 11930 11940 11950
11960 11970 11980 11990 12000
12010 12020 12030 12040 12050
12060 12070 12080 12090 12100
12110 12120 12130 12140 12150
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq

FIGURE 19Z

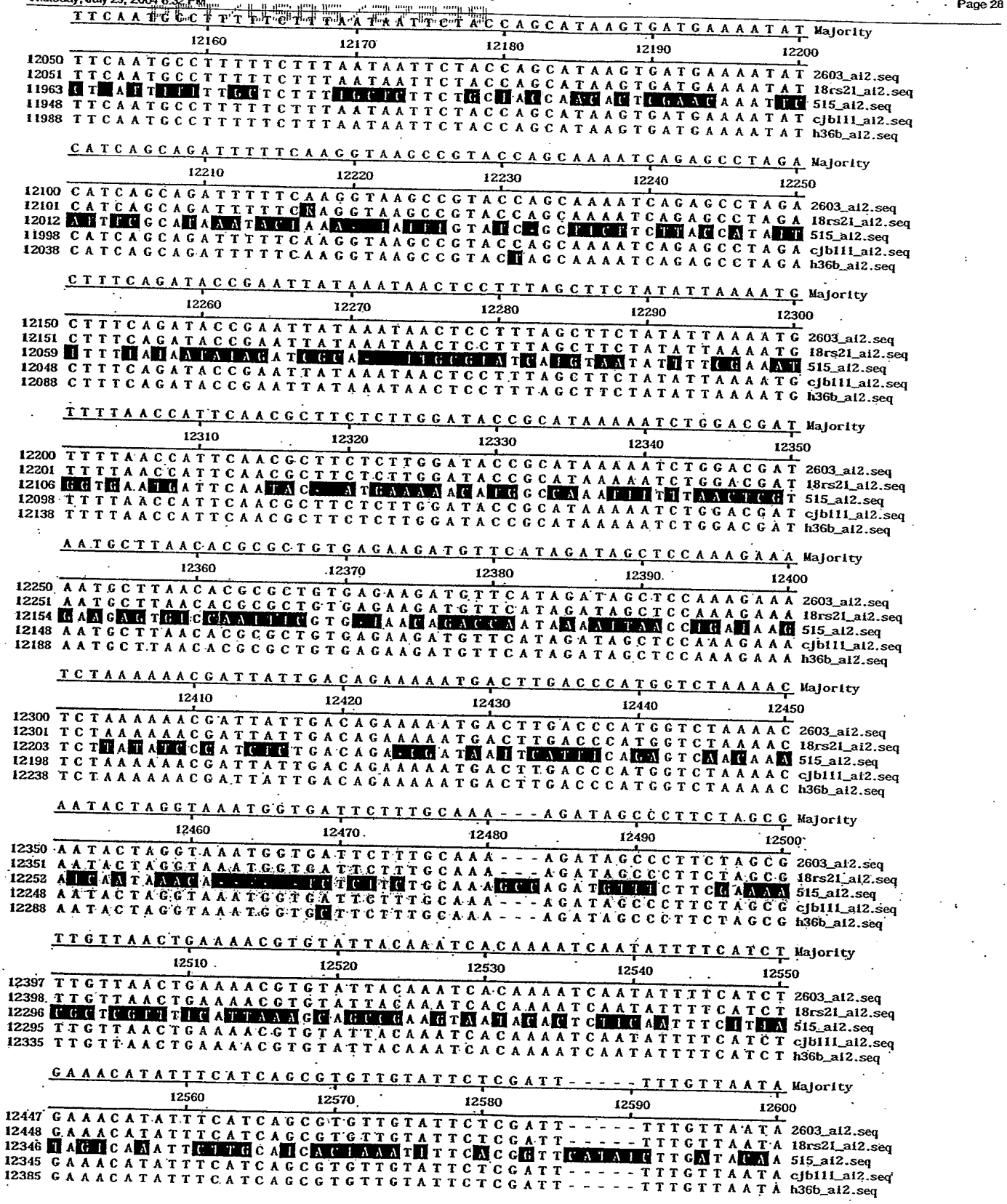

Majority
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq

FIGURE 19AA

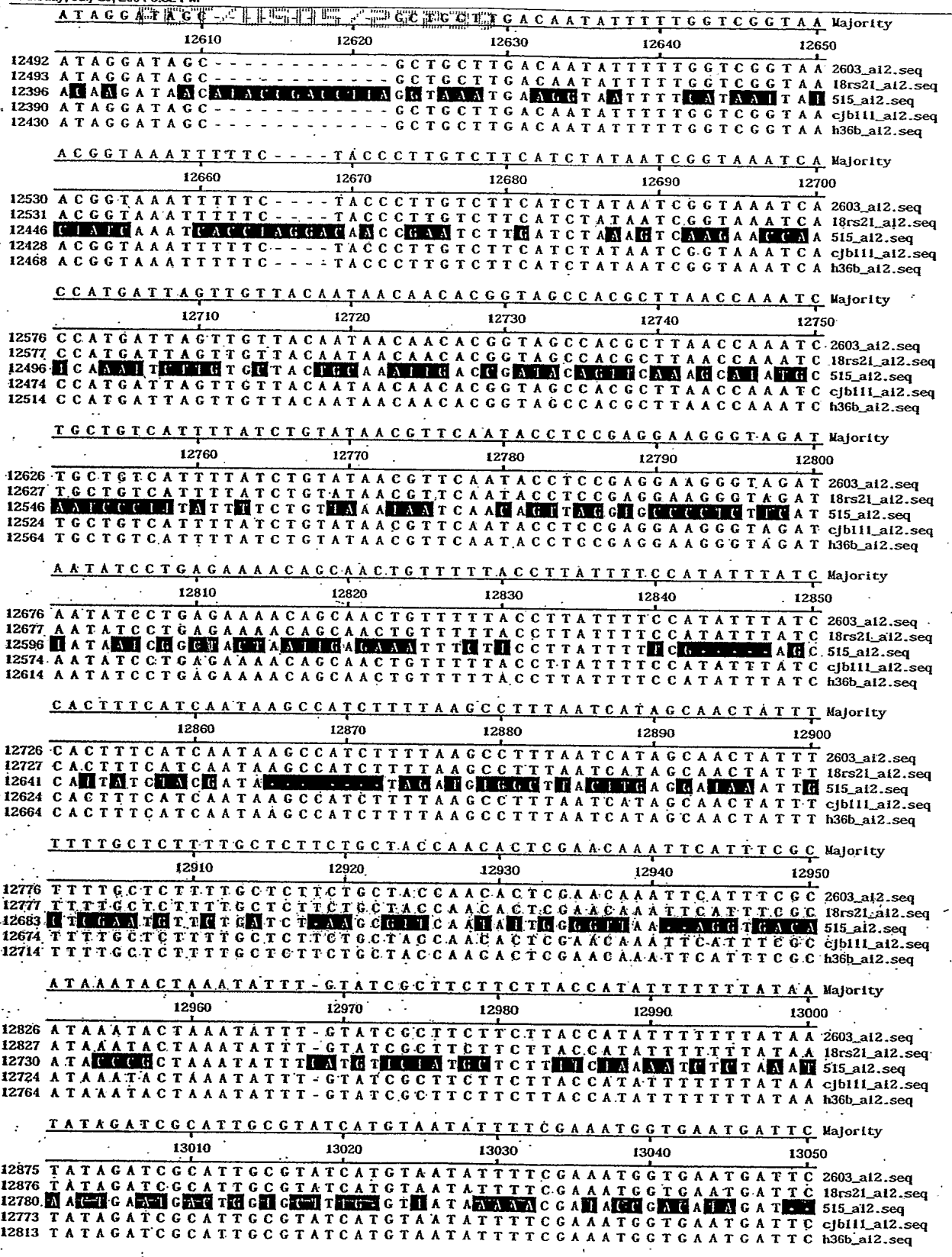

Majority
12610 12620 12630 12640 12650
12492 2603_a12.seq
12493 2603_a12.seq
12396 18rs21_a12.seq
12390 515_a12.seq
12430 cjb111_a12.seq
12430 h36b_a12.seq
Majority
12660 12670 12680 12690 12700
12530 2603_a12.seq
12531 2603_a12.seq
12446 18rs21_a12.seq
12428 515_a12.seq
12468 cjb111_a12.seq
12468 h36b_a12.seq
Majority
12710 12720 12730 12740 12750
12576 2603_a12.seq
12577 2603_a12.seq
12496 18rs21_a12.seq
12474 515_a12.seq
12514 cjb111_a12.seq
12514 h36b_a12.seq
Majority
12760 12770 12780 12790 12800
12626 2603_a12.seq
12627 2603_a12.seq
12546 18rs21_a12.seq
12524 515_a12.seq
12564 cjb111_a12.seq
12564 h36b_a12.seq
Majority
12810 12820 12830 12840 12850
12676 2603_a12.seq
12677 2603_a12.seq
12596 18rs21_a12.seq
12574 515_a12.seq
12614 cjb111_a12.seq
12614 h36b_a12.seq
Majority
12860 12870 12880 12890 12900
12726 2603_a12.seq
12727 2603_a12.seq
12641 18rs21_a12.seq
12624 515_a12.seq
12664 cjb111_a12.seq
12664 h36b_a12.seq
Majority
12910 12920 12930 12940 12950
12776 2603_a12.seq
12777 2603_a12.seq
12683 18rs21_a12.seq
12674 515_a12.seq
12714 cjb111_a12.seq
12714 h36b_a12.seq
Majority
12960 12970 12980 12990 13000
12826 2603_a12.seq
12827 2603_a12.seq
12730 18rs21_a12.seq
12724 515_a12.seq
12764 cjb111_a12.seq
12764 h36b_a12.seq
Majority
13010 13020 13030 13040 13050
12875 2603_a12.seq
12876 2603_a12.seq
12780 18rs21_a12.seq
12773 515_a12.seq
12813 cjb111_a12.seq
12813 h36b_a12.seq

FIGURE 19AB

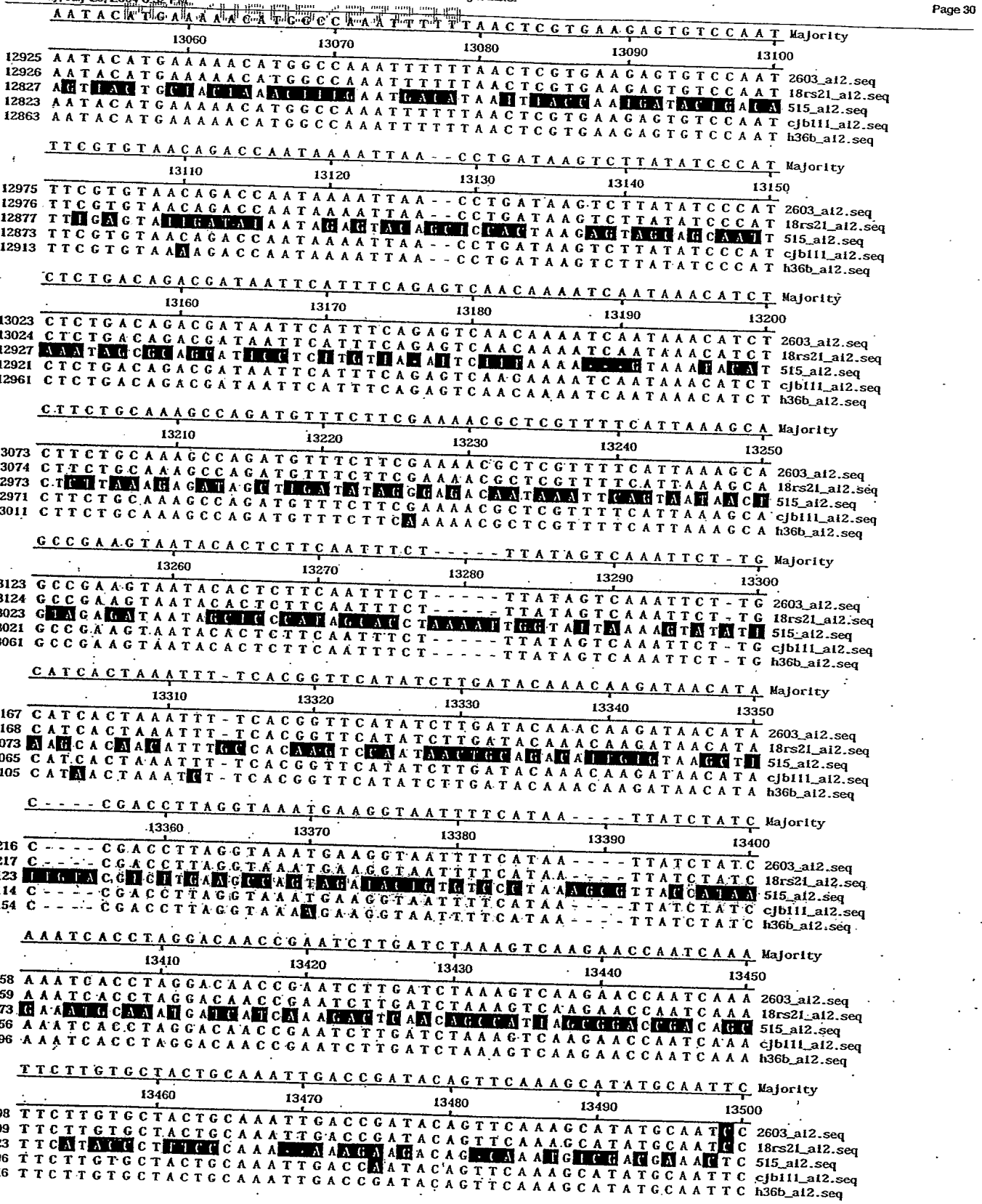
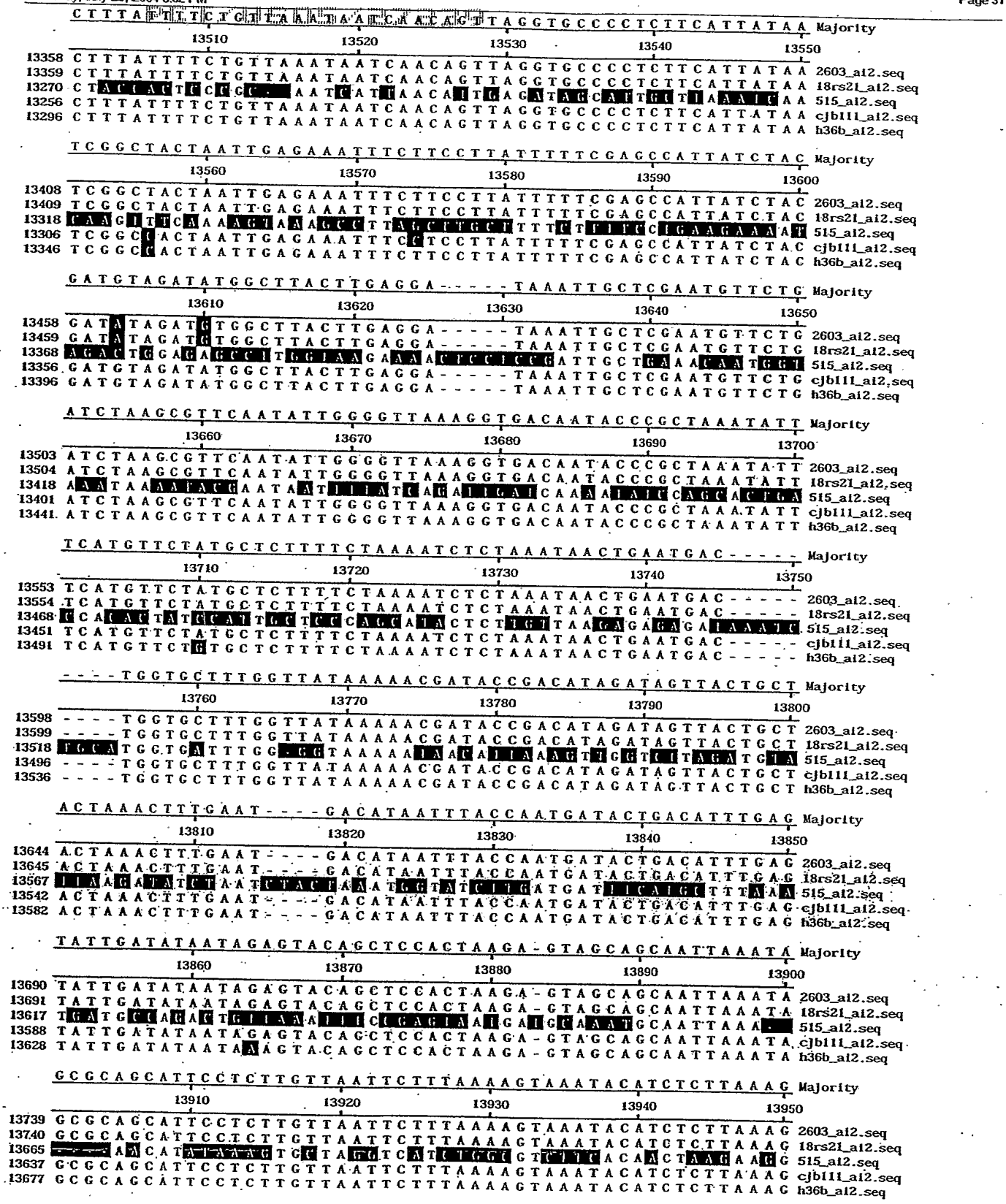

Majority
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq

FIGURE 19AC


Majority
13510
13520
13530
13540
13550
2603_a12.seq
18rs21_a12.seq
515_a12.seq
cjb111_a12.seq
h36b_a12.seq
13560
13570
13580
13590
13600
13610
13620
13630
13640
13650
13660
13670
13680
13690
13700
13710
13720
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13740
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13790
13800
13810
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13900
13910
13920
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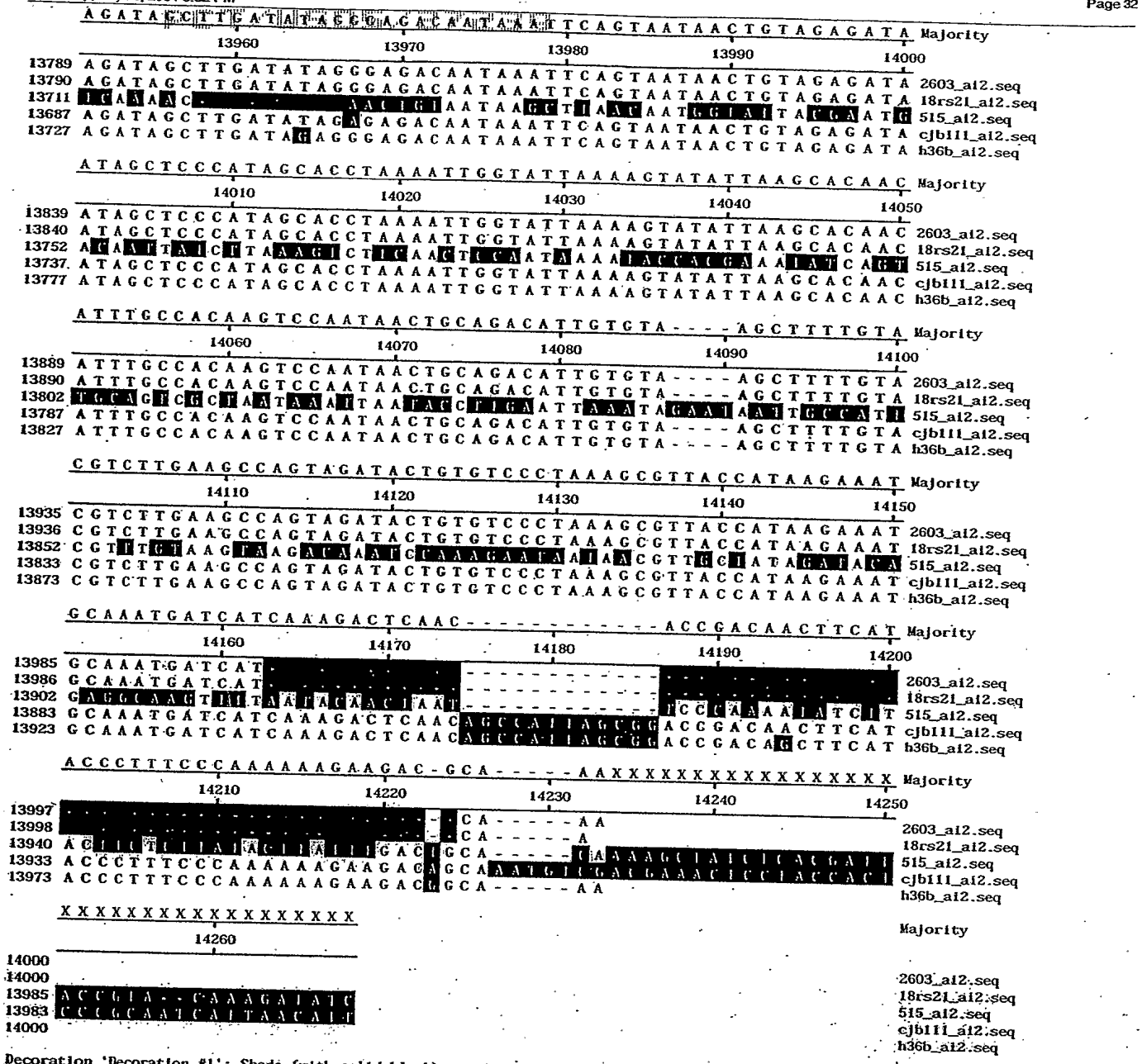
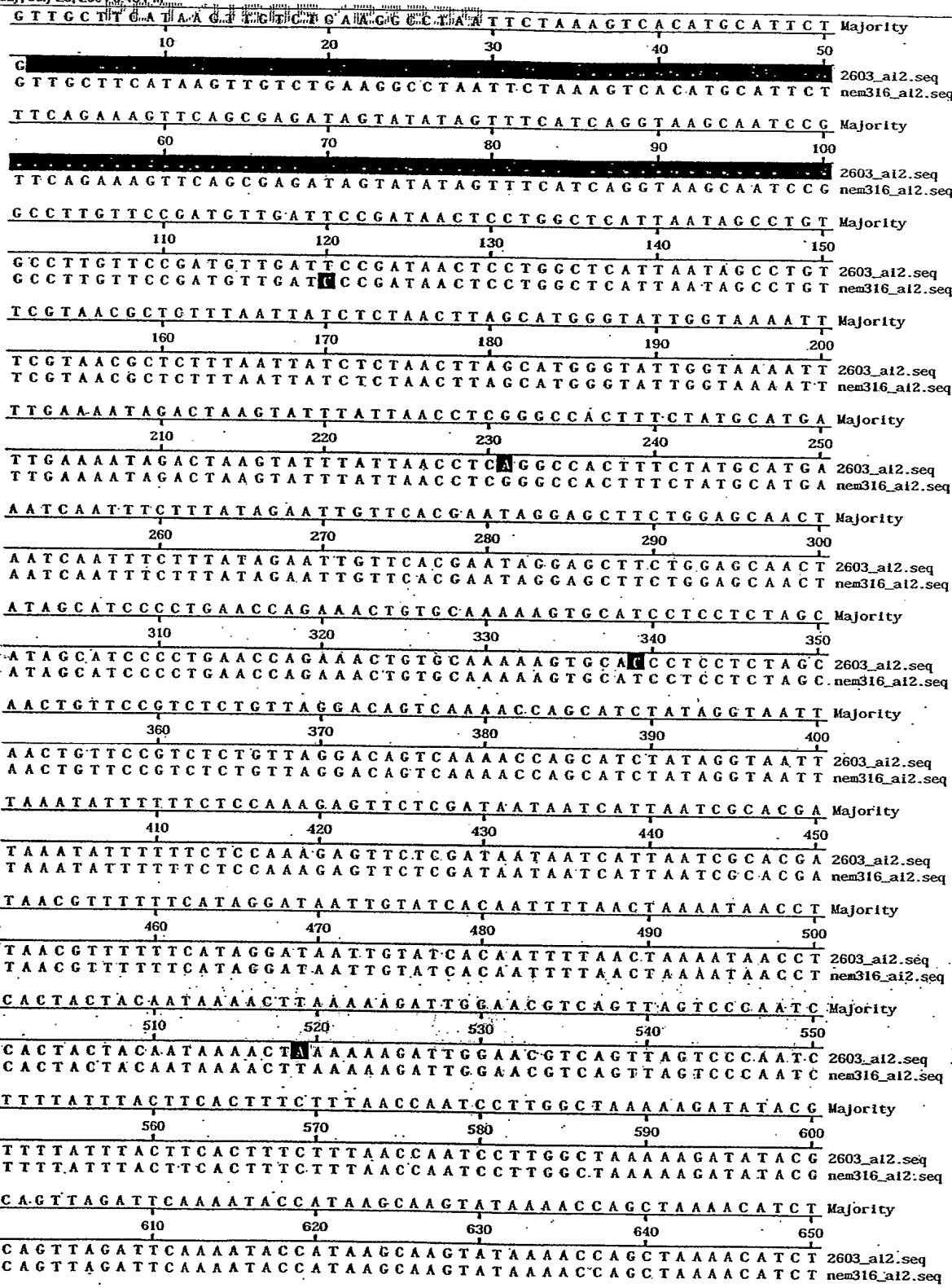
13940
13950

FIGURE 19AD



Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

FIGURE 19AE


GTTGCTTCATAAGTTGTCTGAAGGCCTAATTCTAAAGTCACATGCATTCT Majority
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1 G
1 GTTGCTTCATAAGTTGTCTGAAGGCCTAATTCTAAAGTCACATGCATTCT 2603_a12.seq
nem316_a12.seq
TTCAGAAAGTTCAGCGAGATAGTATATAGTTTCATCAGGTAAGCAATCCG Majority
60 70 80 90 100
2
51 TTCAGAAAGTTCAGCGAGATAGTATATAGTTTCATCAGGTAAGCAATCCG 2603_a12.seq
nem316_a12.seq
GCCTTGTTCCGATGTTGATTCCGATAACTCCTGGCTCATTAATAGCCTGT Majority
110 120 130 140 150
2 GCCTTGTTCCGATGTTGATTCCGATAACTCCTGGCTCATTAATAGCCTGT 2603_a12.seq
101 GCCTTGTTCCGATGTTGATCCCGATAACTCCTGGCTCATTAATAGCCTGT nem316_a12.seq
TCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAATT Majority
160 170 180 190 200
52 TCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAATT 2603_a12.seq
151 TCGTAACGCTCTTTAATTATCTCTAACTTAGCATGGGTATTGGTAAAATT nem316_a12.seq
TTGAAAATAGACTAAGTATTTATTAACCTCGGGCCACTTTCTATGCATGA Majority
210 220 230 240 250
102 TTGAAAATAGACTAAGTATTTATTAACCTCAGGCCACTTTCTATGCATGA 2603_a12.seq
201 TTGAAAATAGACTAAGTATTTATTAACCTCGGGCCACTTTCTATGCATGA nem316_a12.seq
AATCAATTTCTTTATAGAATTGTTCACGAATAGGAGCTTCTGGAGCAACT Majority
260 270 280 290 300
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251 AATCAATTTCTTTATAGAATTGTTCACGAATAGGAGCTTCTGGAGCAACT nem316_a12.seq
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Figure 20

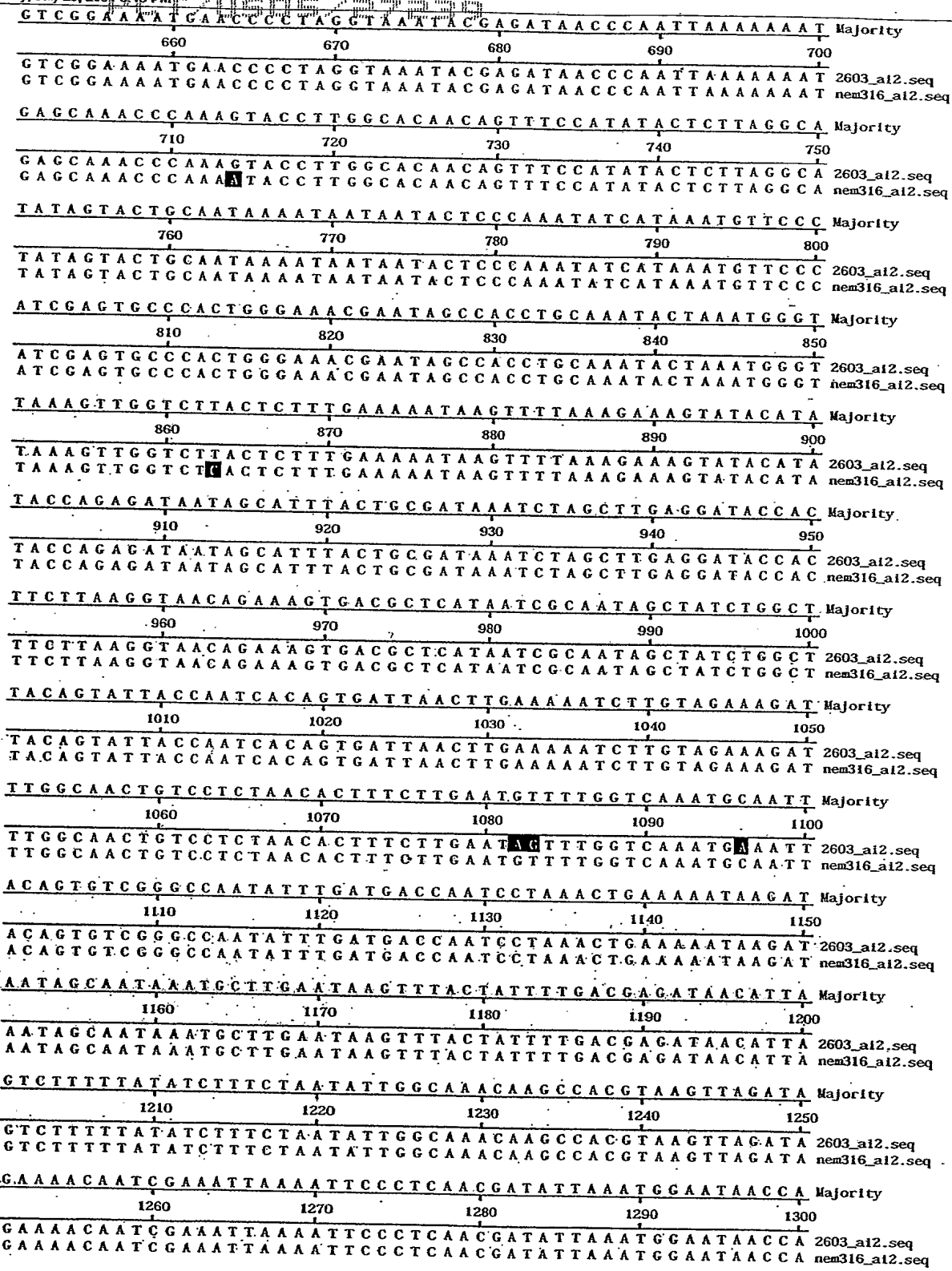
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FIGURE 20A

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FIGURE 20B

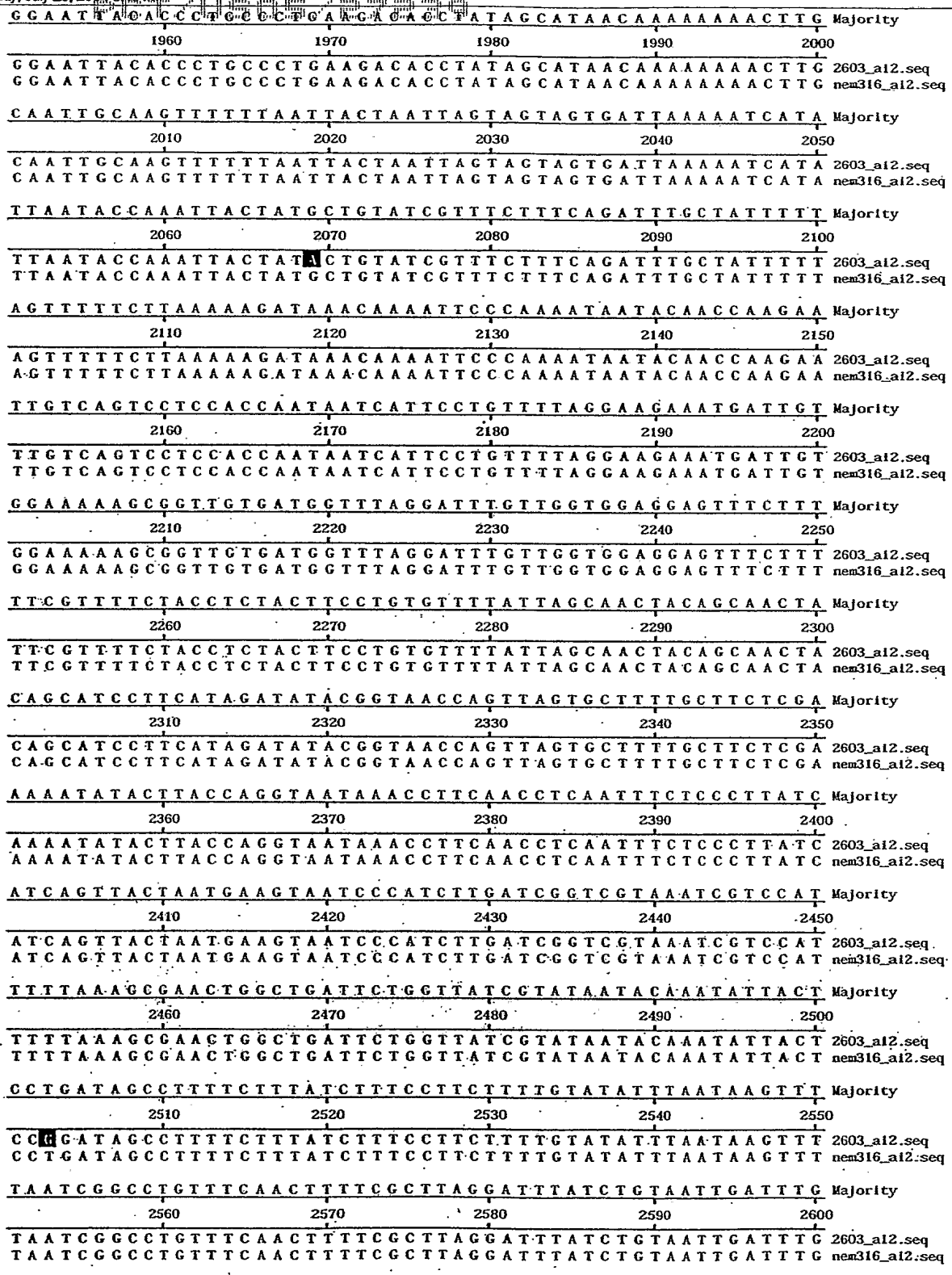
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FIGURE 20C

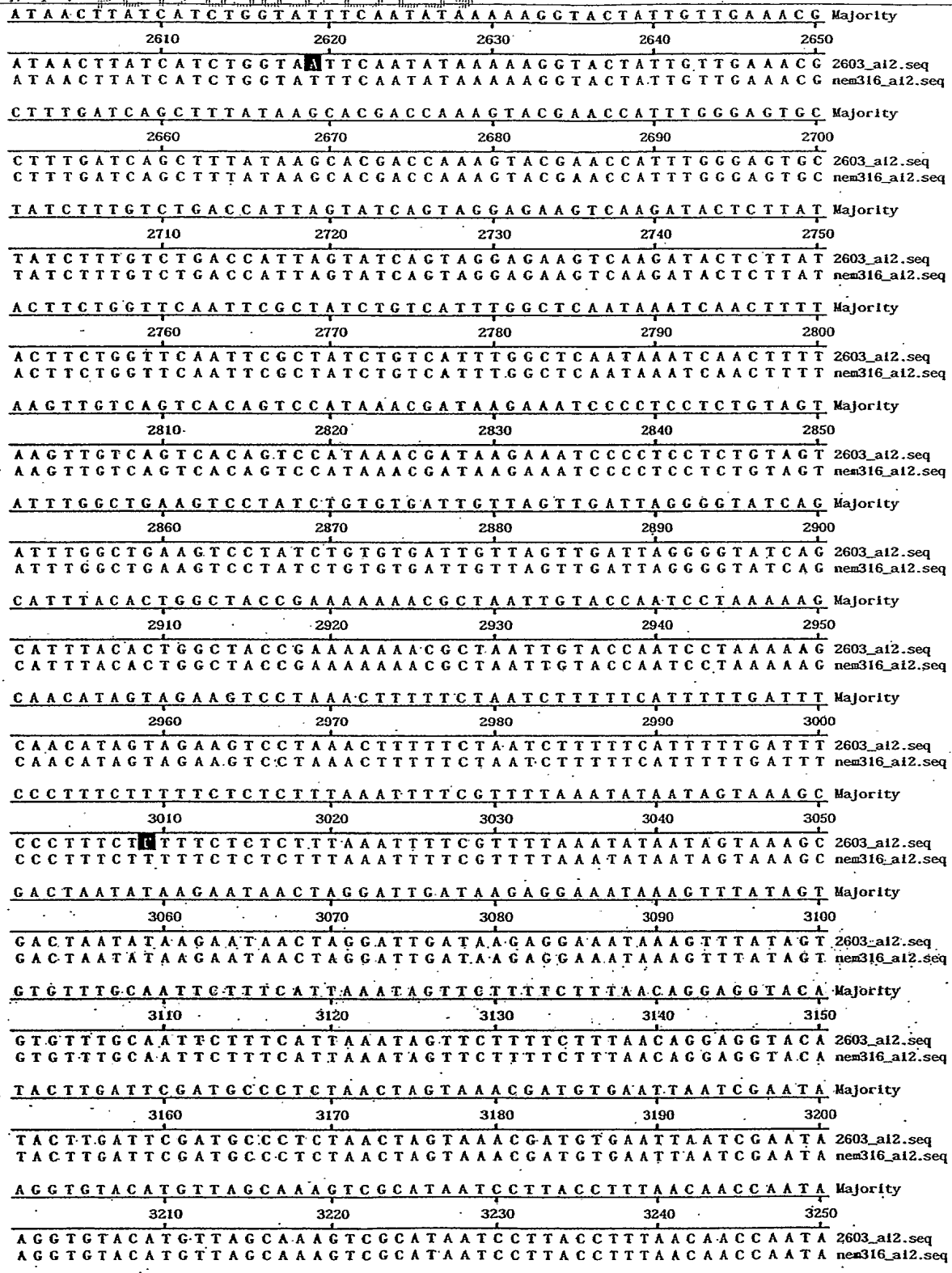
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FIGURE 20D

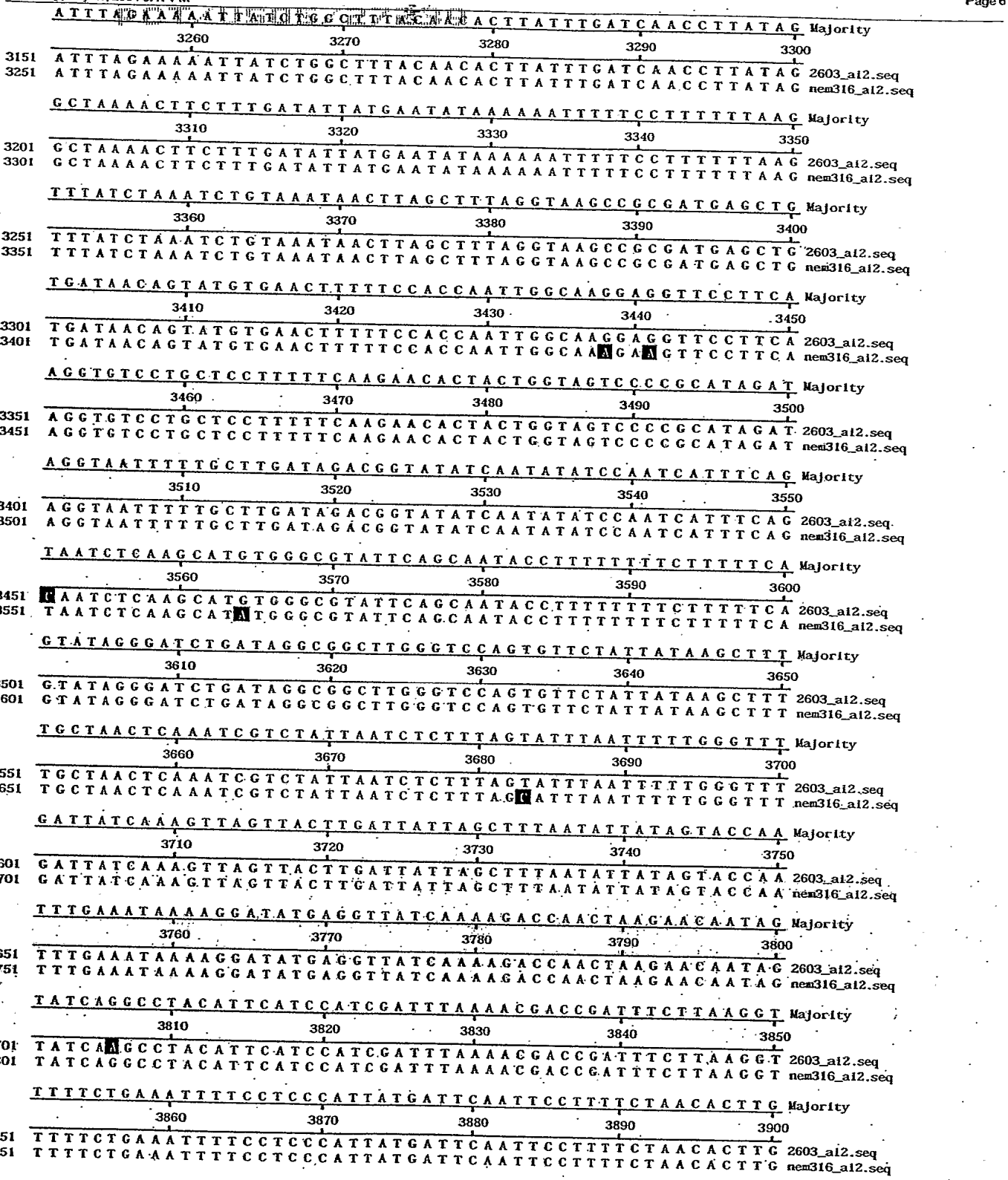
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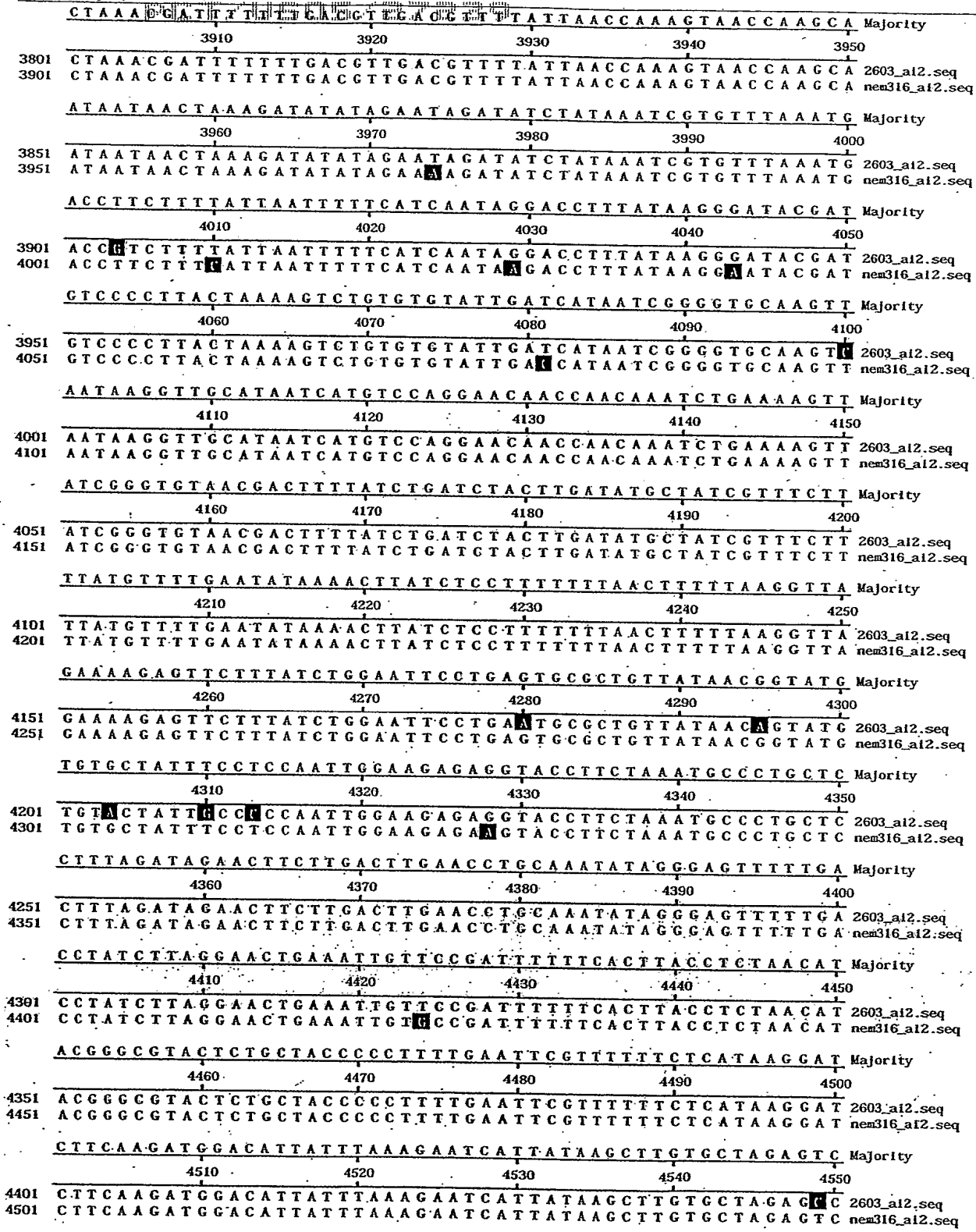
FIGURE 20E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GTCCCCTTACTAAAAGTCTGTGTGTATTGATCATAATCGGGGTGCAAGTT Majority
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FIGURE 20F

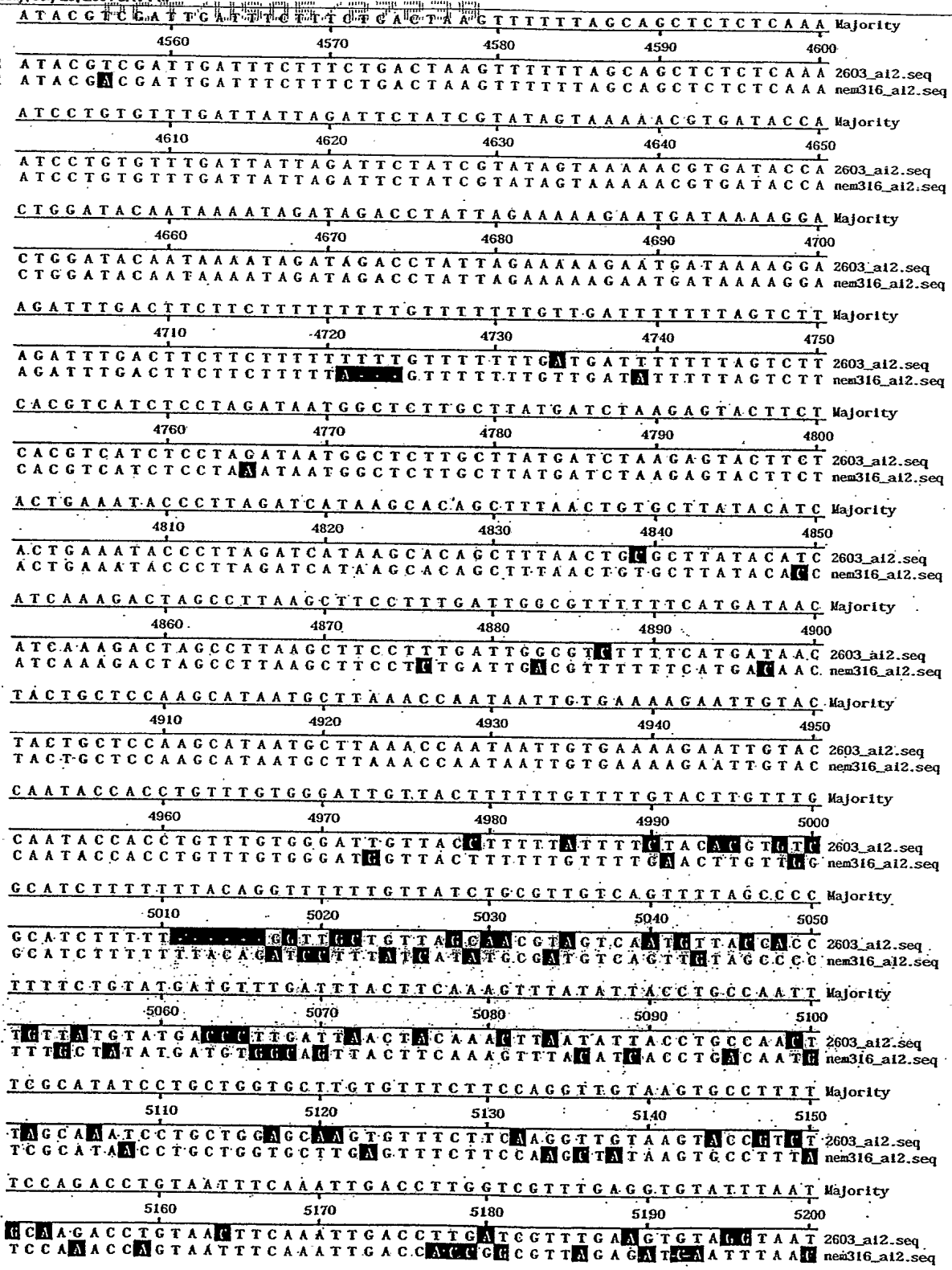
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FIGURE 20G

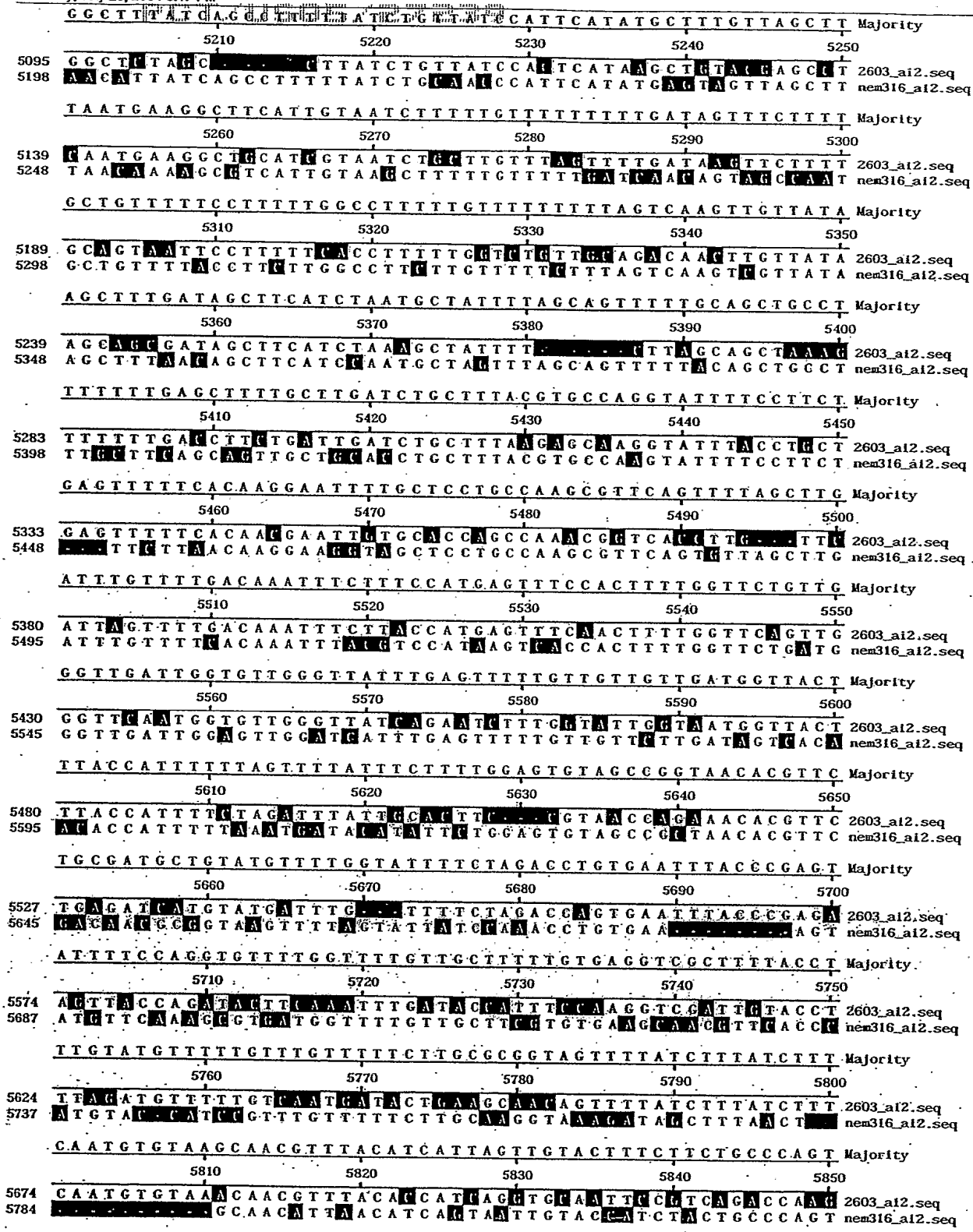


FIGURE 20H

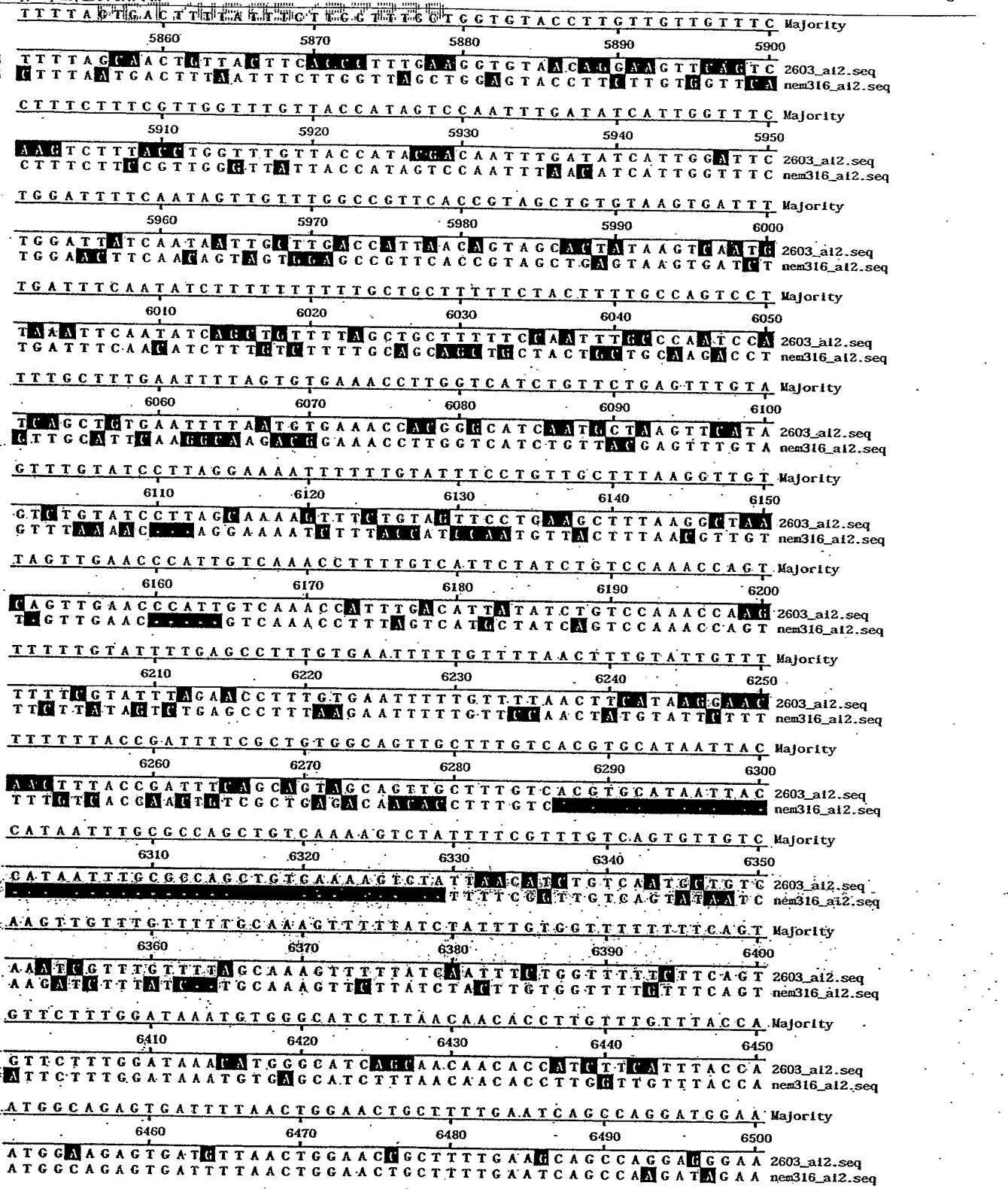
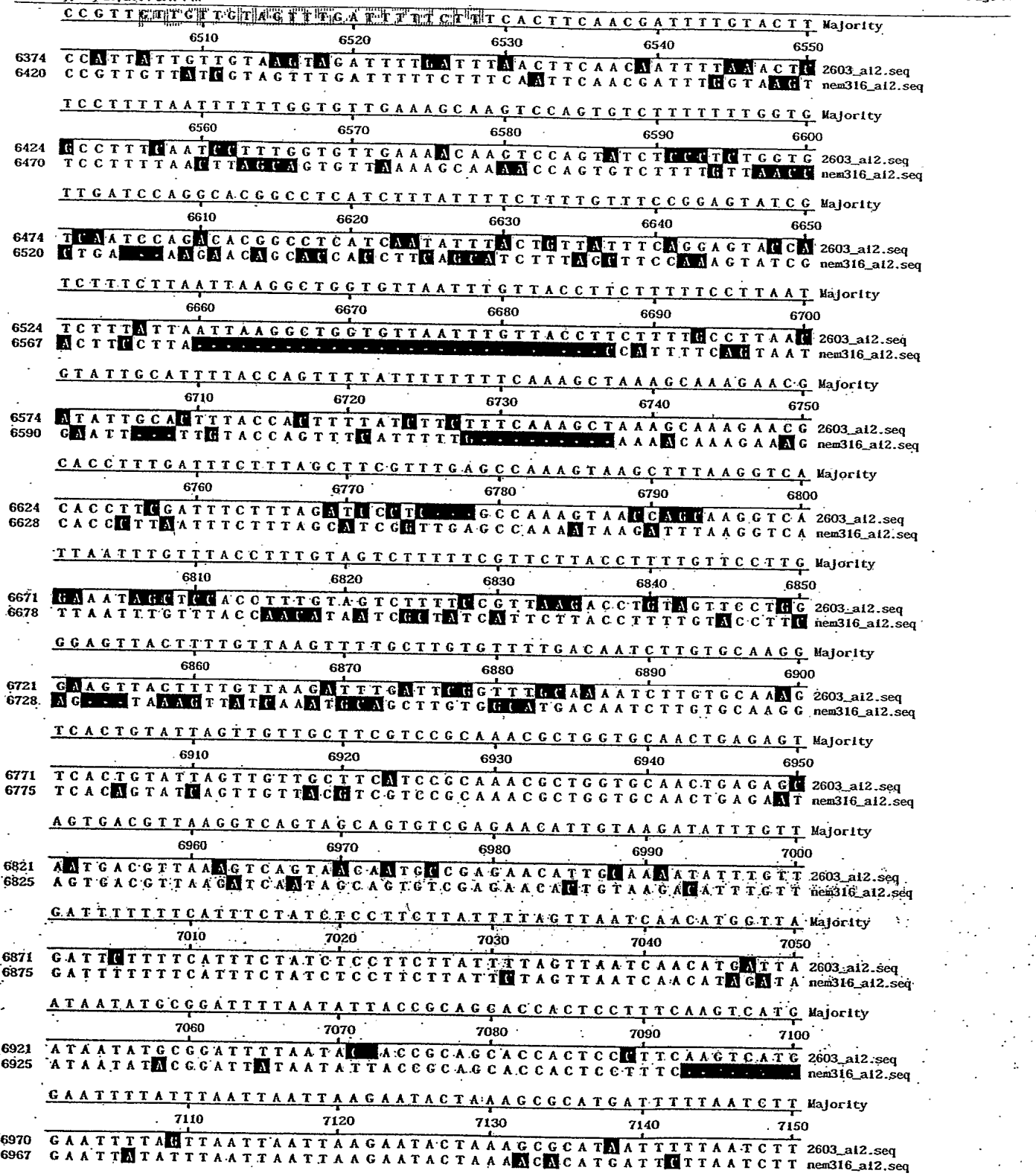


FIGURE 20I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Majority
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6474 2603_a12.seq
6520 nem316_a12.seq
Majority
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Majority
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6574 2603_a12.seq
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Majority
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6624 2603_a12.seq
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Majority
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6671 2603_a12.seq
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Majority
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6775 nem316_a12.seq
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Majority
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6871 2603_a12.seq
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Majority
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6921 2603_a12.seq
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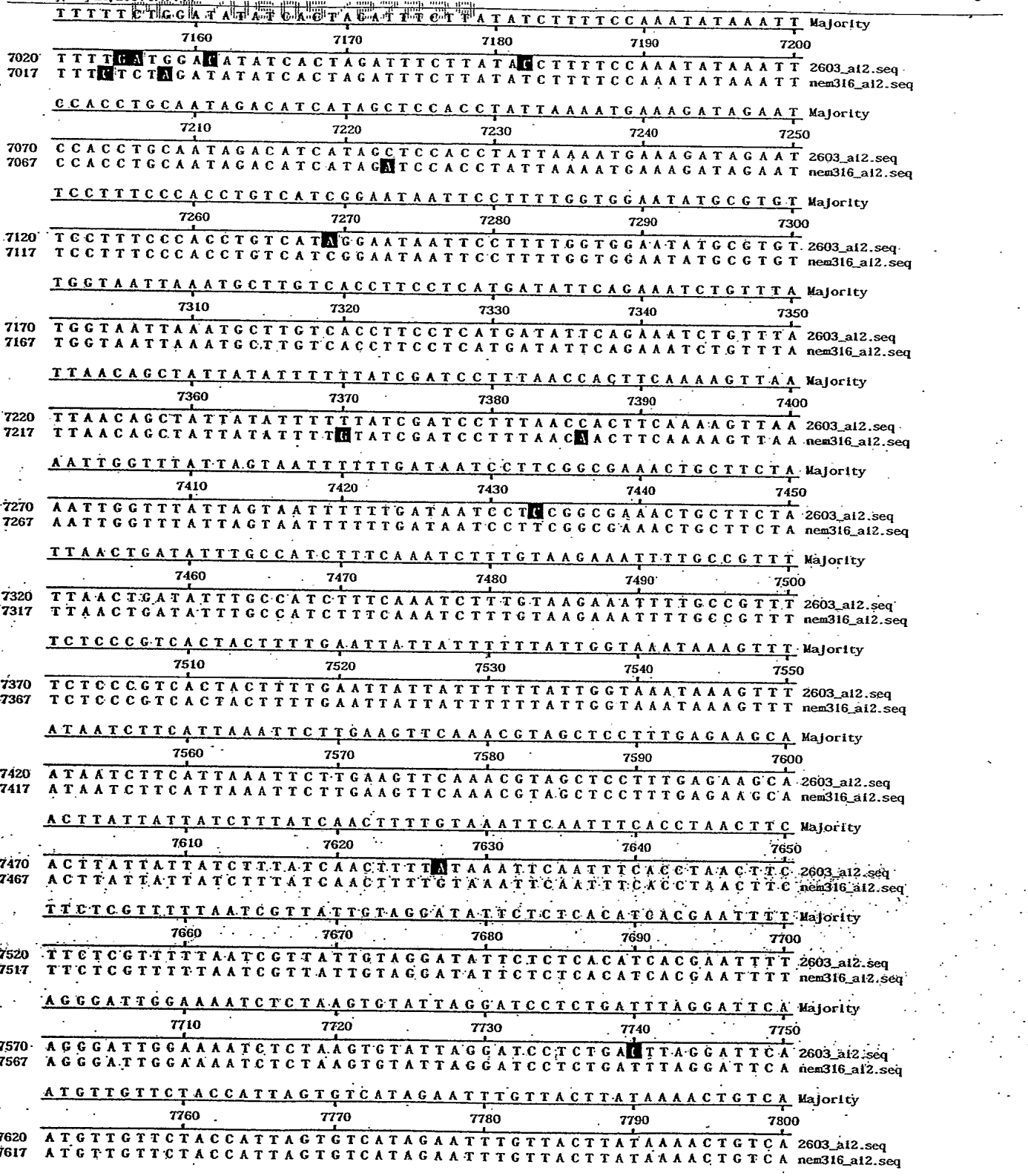
FIGURE 20J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7760 7770 7780 7790 7800
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FIGURE 20K

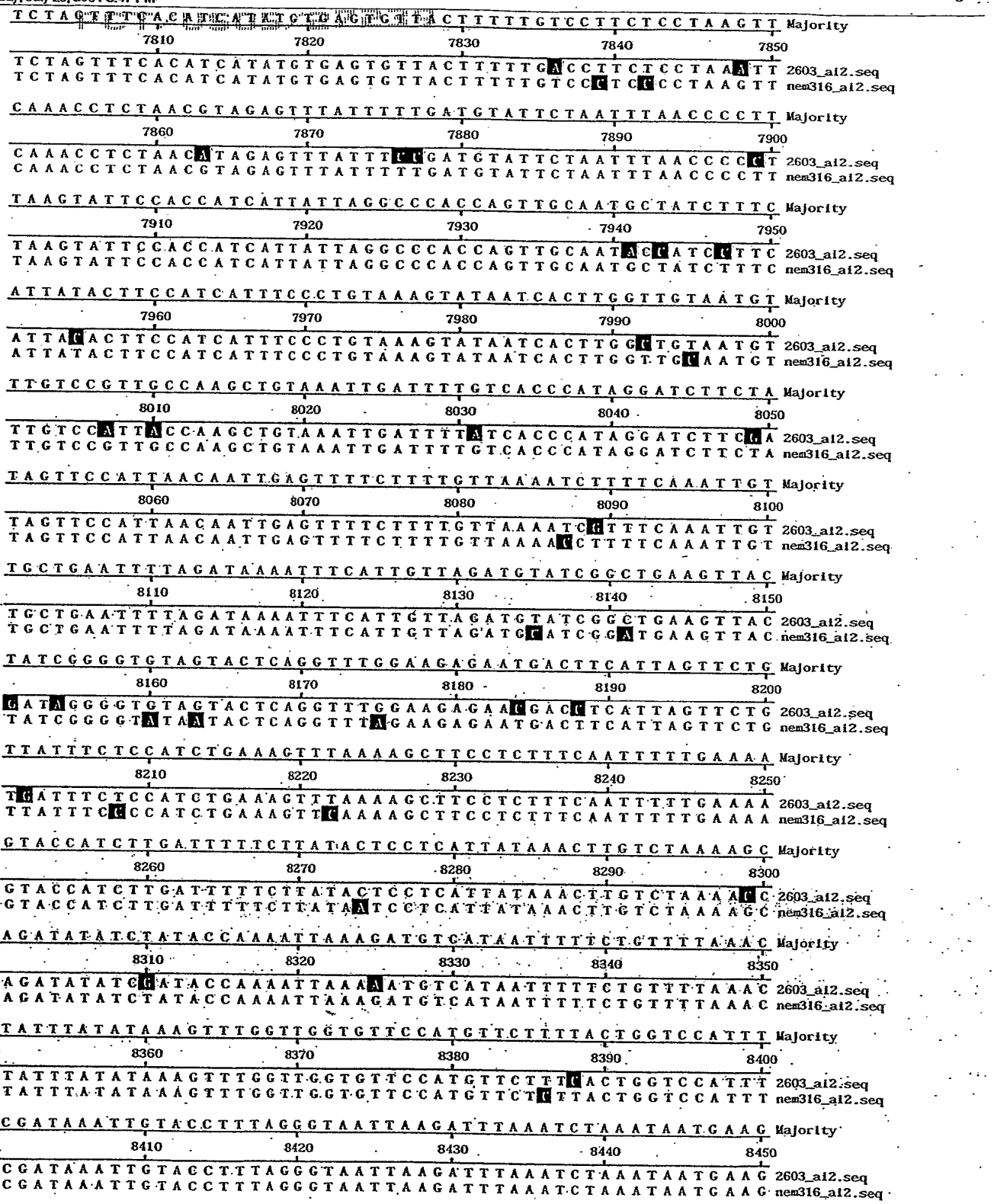

FIGURE 20L

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8517  TTGTTGGAACACCATCAGTTATATGAACAATAATTTTTTGACTATTTCGA nem316_al2.seq

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FIGURE 20M

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FIGURE 20N

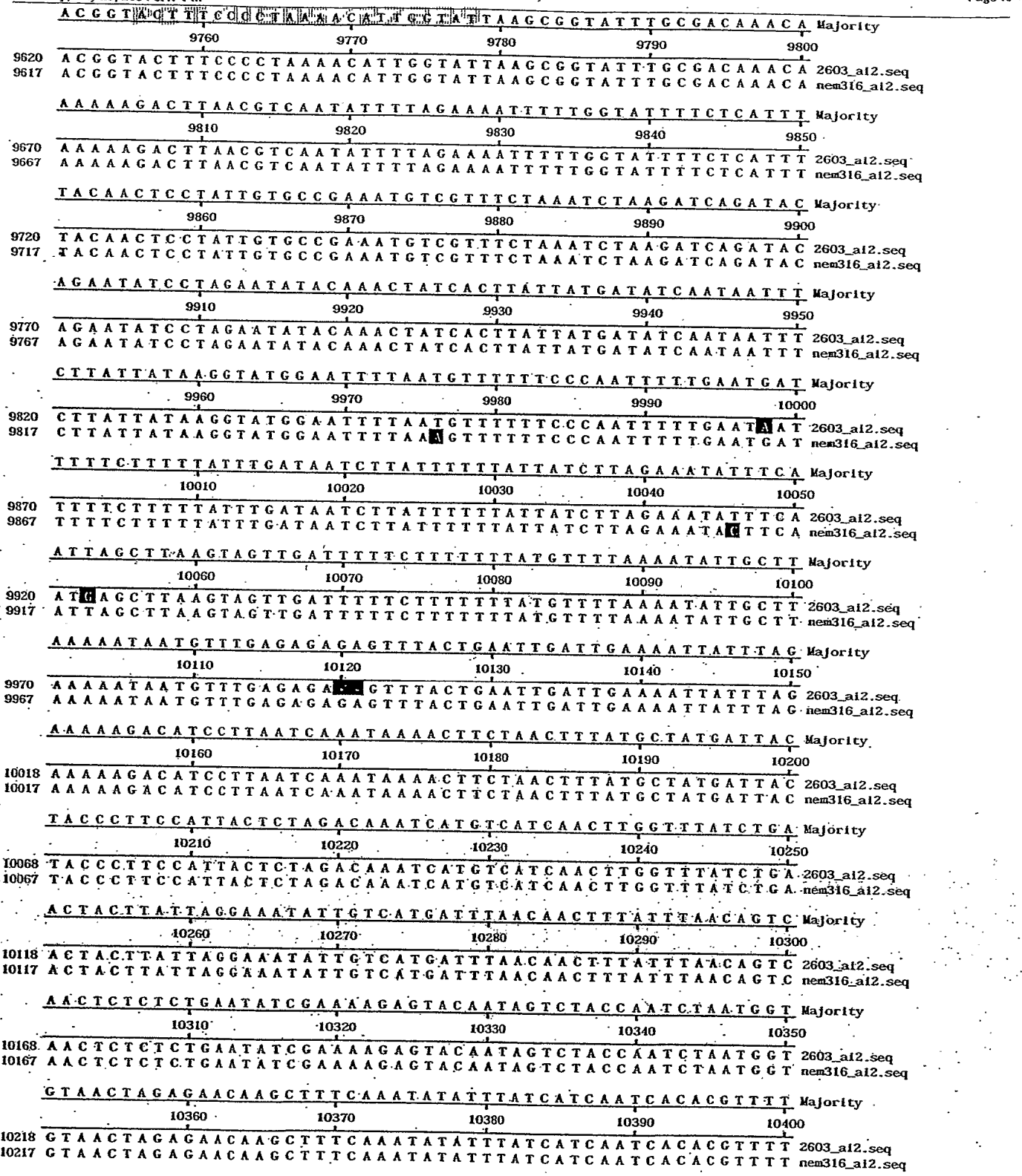
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FIGURE 20O

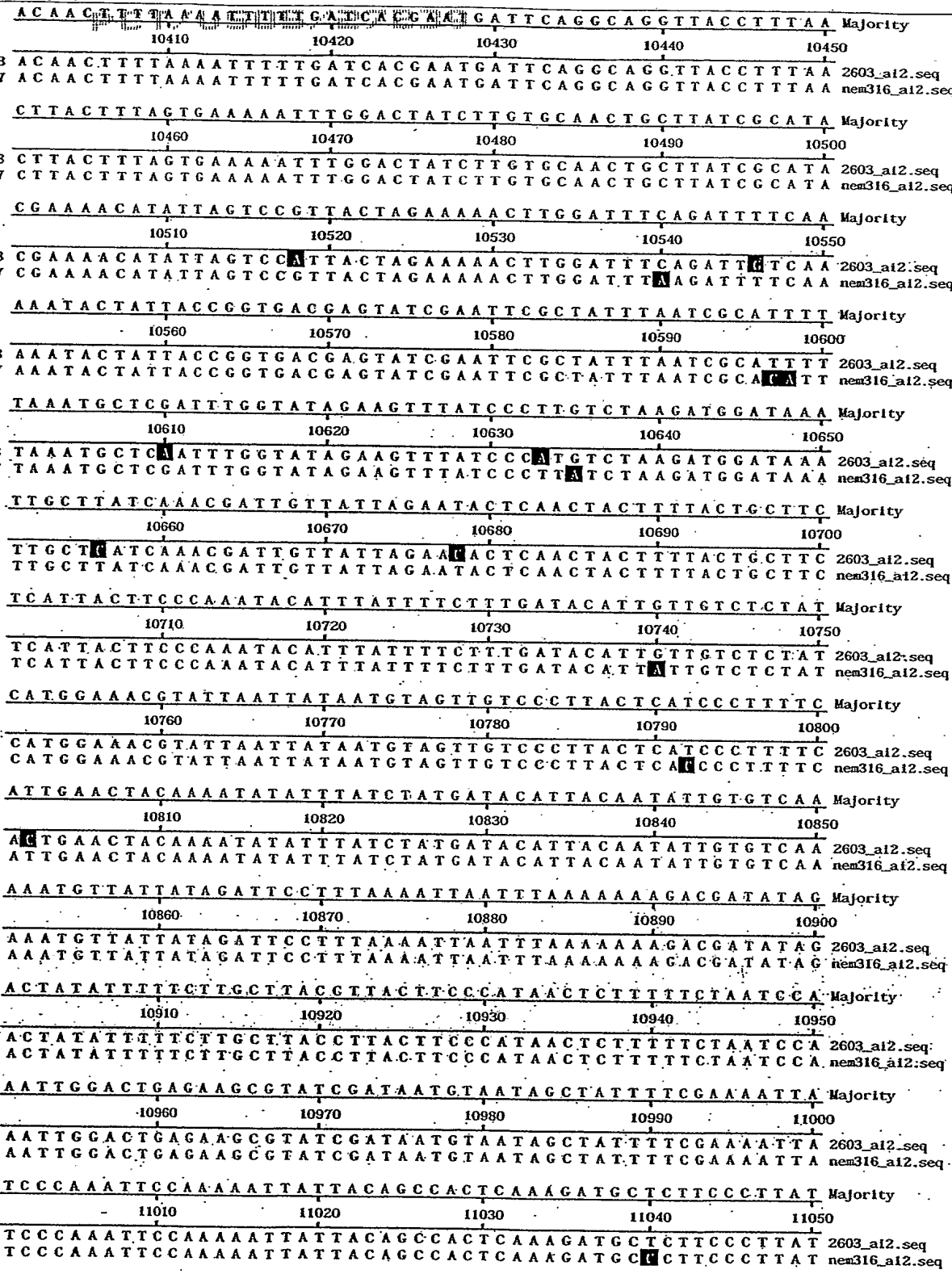
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FIGURE 20P

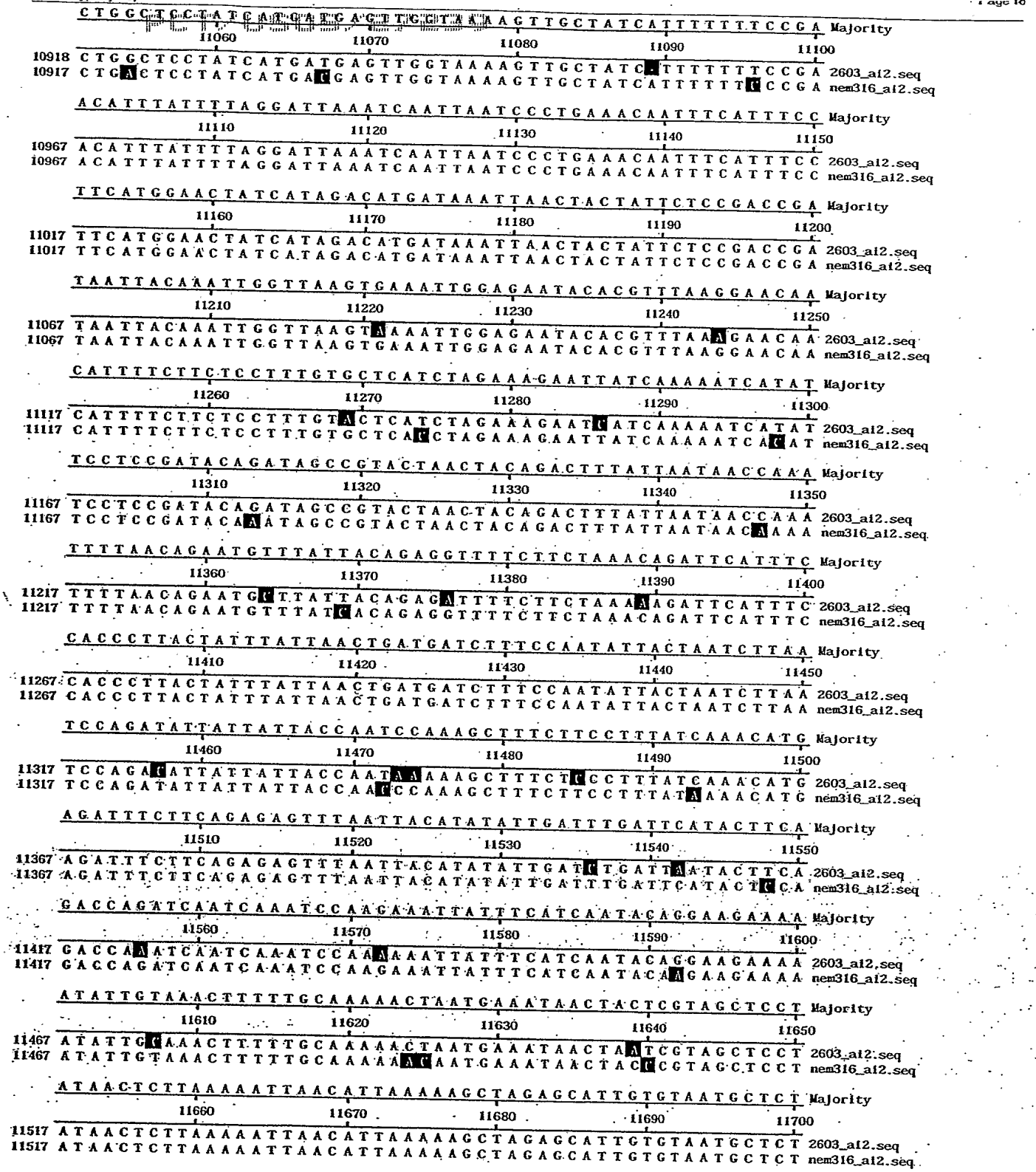
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FIGURE 20Q

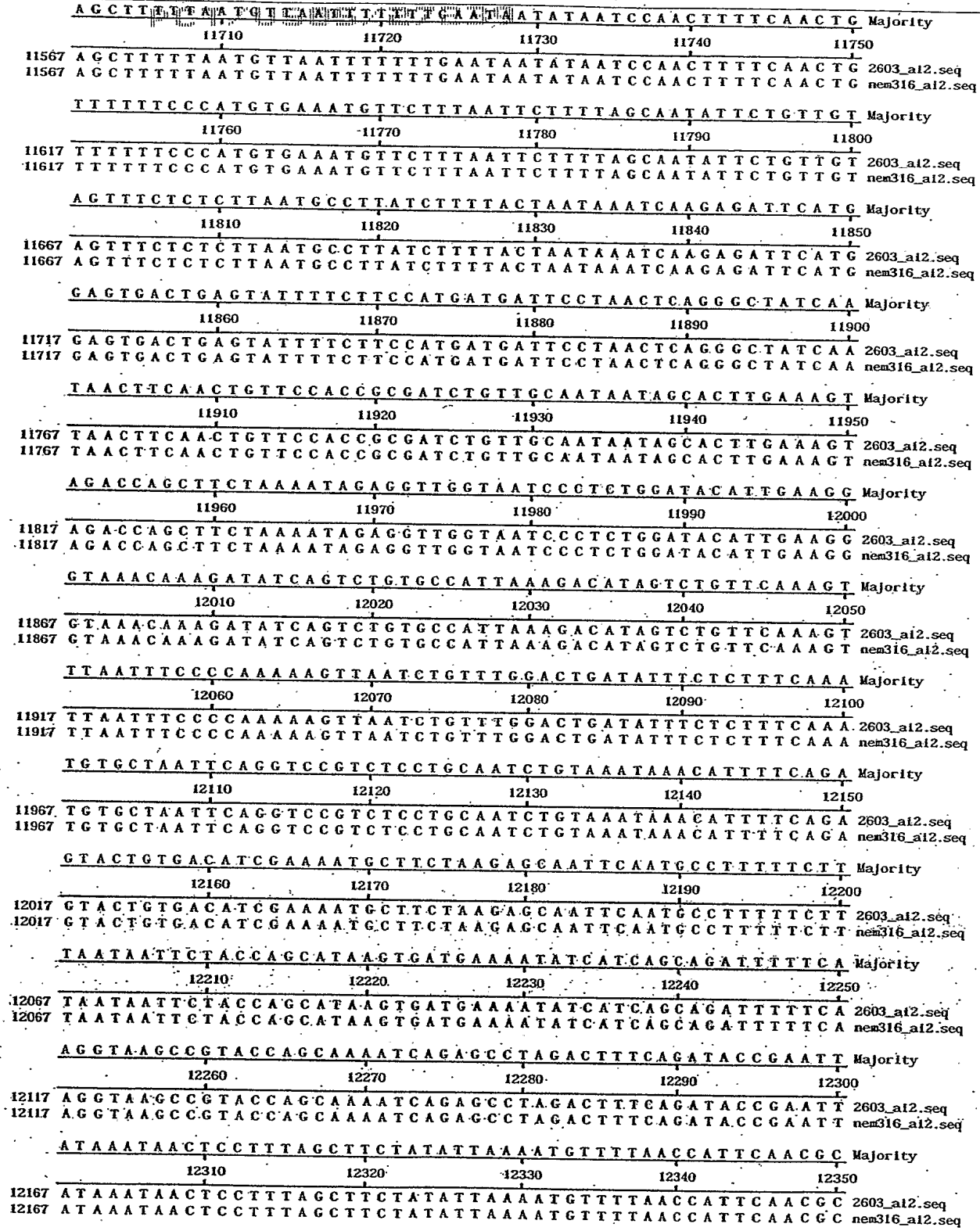
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FIGURE 20R

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TCATTTCGCATAAATACTAAATATTTGTATCGCTTCTTCTTACCATATTT Majority
          12960     12970     12980     12990     13000
12817 TCATTTCGCATAAATACTAAATATTTGTATCGCTTCTTCTTACCATATTT 2603_a12.seq
12817 TCATTTCGCATAAATACTAAATATTTGTATCGCTTCTTCTTACCATATTT nem316_a12.seq
```

FIGURE 20S

```
TTTTATAATATAGATCGCATTGCGTATCATGTAATATTTTCGAAATGGTG Majority
          13010     13020     13030     13040     13050
12867 TTTTATAATATAGATCGCATTGCGTATCATGTAATATTTTCGAAATGGTG 2603_a12.seq
12867 TTTTATAATATAGATCGCATTGCGTATCATGTAATATTTTCGAAATGGTG nem316_a12.seq

AATGATTCAATACATGAAAAACATGGCCAAATTTTTTAACTCGTGAAGAG Majority
          13060     13070     13080     13090     13100
12917 AATGATTCAATACATGAAAAACATGGCCAAATTTTTTAACTCGTGAAGAG 2603_a12.seq
12917 AATGATTCAATACATGAAAAACATGGCCAAATTTTTTAACTCGTGAAGAG nem316_a12.seq

TGTCCAATTTCGTGTAACAGACCAATAAAATTAACCTGATAAGTCTTATA Majority
          13110     13120     13130     13140     13150
12967 TGTCCAATTTCGTGTAACAGACCAATAAAATTAACCTGATAAGTCTTATA 2603_a12.seq
12967 TGTCCAATTTCGTGTAACAGACCAATAAAATTAACCTGATAAGTCTTATA nem316_a12.seq

TCCCATCTCTGACAGACGATAATTCATTTCAGAGTCAACAAAATCAATAA Majority
          13160     13170     13180     13190     13200
13017 TCCCATCTCTGACAGACGATAATTCATTTCAGAGTCAACAAAATCAATAA 2603_a12.seq
13017 TCCCATCTCTGACAGACGATAATTCATTTCAGAGTCAACAAAATCAATAA nem316_a12.seq

ACATCTCTTCTGCAAAGCCAGATGTTTCTTCGAAAACGCTCGTTTTCATT Majority
          13210     13220     13230     13240     13250
13067 ACATCTCTTCTGCAAAGCCAGATGTTTCTTCGAAAACGCTCGTTTTCATT 2603_a12.seq
13067 ACATCTCTTCTGCAAAGCCAGATGTTTCTTCGAAAACGCTCGTTTTCATT nem316_a12.seq

AAAGCAGCCGAAGTAATACACTCTTCAATTTCTTTATAGTCAAATTCTTG Majority
          13260     13270     13280     13290     13300
13117 AAAGCAGCCGAAGTAATACACTCTTCAATTTCTTTATAGTCAAATTCTTG 2603_a12.seq
13117 AAAGCAGCCGAAGTAATACACTCTTCAATTTCTTTATAGTCAAATTCTTG nem316_a12.seq

CATCACTAAATTTTCACGGTTCATATCTTGATACAAACAAGATAACATAC Majority
          13310     13320     13330     13340     13350
13167 CATCACTAAATTTTCACGGTTCATATCTTGATACAAACAAGATAACATAC 2603_a12.seq
13167 CATCACTAAATTTTCACGGTTCATATCTTGATACAAACAAGATAACATAC nem316_a12.seq

CGACCTTAGGTAAATGAAGGTAATTTTCATAATTATCTATCAAATCACCT Majority
          13360     13370     13380     13390     13400
13217 CGACCTTAGGTAAATGAAGGTAATTTTCATAATTATCTATCAAATCACCT 2603_a12.seq
13217 CGACCTTAGGTAAATGAAGGTAATTTTCATAATTATCTATCAAATCACCT nem316_a12.seq

AGGACAACCGAATCTTGATCTAAAGTCAAGAACCAATCAAATTCTTGTGC Majority
          13410     13420     13430     13440     13450
13267 AGGACAACCGAATCTTGATCTAAAGTCAAGAACCAATCAAATTCTTGTGC 2603_a12.seq
13267 AGGACAACCGAATCTTGATCTAAAGTCAAGAACCAATCAAATTCTTGTGC nem316_a12.seq

TACTGCAAATTGACCGATACAGTTCAAAGCATATGCAATCCCTTTATTTT Majority
          13460     13470     13480     13490     13500
13317 TACTGCAAATTGACCGATACAGTTCAAAGCATATGCAATCCCTTTATTTT 2603_a12.seq
13317 TACTGCAAATTGACCGATACAGTTCAAAGCATATGCAATCCCTTTATTTT nem316_a12.seq

CTGTTAAATAATCAACAGTTAGGTGCCCCTCTTCATTATAATCGGCTACT Majority
          13510     13520     13530     13540     13550
13367 CTGTTAAATAATCAACAGTTAGGTGCCCCTCTTCATTATAATCGGCTACT 2603_a12.seq
13367 CTGTTAAATAATCAACAGTTAGGTGCCCCTCTTCATTATAATCGGCTACT nem316_a12.seq

AATTGAGAAATTTCTTCCTTATTTTTCGAGCCATTATCTACGATATAGAT Majority
          13560     13570     13580     13590     13600
13417 AATTGAGAAATTTCTTCCTTATTTTTCGAGCCATTATCTACGATATAGAT 2603_a12.seq
13417 AATTGAGAAATTTCTTCCTTATTTTTCGAGCCATTATCTACGATATAGAT nem316_a12.seq

GTGGCTTACTTGAGGATAAATTGCTCGAATGTTCTGATCTAAGCGTTCAA Majority
          13610     13620     13630     13640     13650
13467 GTGGCTTACTTGAGGATAAATTGCTCGAATGTTCTGATCTAAGCGTTCAA 2603_a12.seq
13467 GTGGCTTACTTGAGGATAAATTGCTCGAATGTTCTGATCTAAGCGTTCAA nem316_a12.seq
```

FIGURE 20T

```
      TATTGGGGTTAAAGGTGACAATACCCGCTAAATATTTCATGTTCTATGCT Majority
               13660     13670     13680     13690     13700
13517 TATTGGGGTTAAAGGTGACAATACCCGCTAAATATTTCATGTTCTATGCT 2603_a12.seq
13517 TATTGGGGTTAAAGGTGACAATACCCGCTAAATATTTCATGTTCTATGCT nem316_a12.seq

      CTTTTCTAAAATCTCTAAATAACTGAATGACTGGTGCTTTGGTTATAAAA Majority
               13710     13720     13730     13740     13750
13567 CTTTTCTAAAATCTCTAAATAACTGAATGACTGGTGCTTTGGTTATAAAA 2603_a12.seq
13567 CTTTTCTAAAATCTCTAAATAACTGAATGACTGGTGCTTTGGTTATAAAA nem316_a12.seq

      ACGATACCGACATAGATAGTTACTGCTACTAAACTTTGAATGACATAATT Majority
               13760     13770     13780     13790     13800
13617 ACGATACCGACATAGATAGTTACTGCTACTAAACTTTGAATGACATAATT 2603_a12.seq
13617 ACGATACCGACATAGATAGTTACTGCTACTAAACTTTGAATGACATAATT nem316_a12.seq

      TACCAATGATACTGACATTTGAGTATTGATATAATAGAGTACAGCTCCAC Majority
               13810     13820     13830     13840     13850
13667 TACCAATGATACTGACATTTGAGTATTGATATAATAGAGTACAGCTCCAC 2603_a12.seq
13667 TACCAATGATACTGACATTTGAGTATTGATATAATAGAGTACAGCTCCAC nem316_a12.seq

      TAAGAGTAGCAGCAATTAAATAGCGCAGCATTCCTCTTGTTAATTCTTTA Majority
               13860     13870     13880     13890     13900
13717 TAAGAGTAGCAGCAATTAAATAGCGCAGCATTCCTCTTGTTAATTCTTTA 2603_a12.seq
13717 TAAGAGTAGCAGCAATTAAATAGCGCAGCATTCCTCTTGTTAATTCTTTA nem316_a12.seq

      AAAGTAAATACATCTCTTAAAGAGATAGCTTGATATAGGGAGACAATAAA Majority
               13910     13920     13930     13940     13950
13767 AAAGTAAATACATCTCTTAAAGAGATAGCTTGATATAGGGAGACAATAAA 2603_a12.seq
13767 AAAGTAAATACATCTCTTAAAGAGATAGCTTGATATAGGGAGACAATAAA nem316_a12.seq

      TTCAGTAATAACTGTAGAGATAATAGCTCCCATAGCACCTAAAATTGGTA Majority
               13960     13970     13980     13990     14000
13817 TTCAGTAATAACTGTAGAGATAATAGCTCCCATAGCACCTAAAATTGGTA 2603_a12.seq
13817 TTCAGTAATAACTGTAGAGATAATAGCTCCCATAGCACCTAAAATTGGTA nem316_a12.seq

      TTAAAAGTATATTAAGCACAACATTTGCCACAAGTCCAATAACTGCAGAC Majority
               14010     14020     14030     14040     14050
13867 TTAAAAGTATATTAAGCACAACATTTGCCACAAGTCCAATAACTGCAGAC 2603_a12.seq
13867 TTAAAAGTATATTAAGCACAACATTTGCCACAAGTCCAATAACTGCAGAC nem316_a12.seq

      ATTGTGTAAGCTTTTGTACGTCTTGAAGCCAGTAGATACTGTGTCCCTAA Majority
               14060     14070     14080     14090     14100
13917 ATTGTGTAAGCTTTTGTACGTCTTGAAGCCAGTAGATACTGTGTCCCTAA 2603_a12.seq
13917 ATTGTGTAAGCTTTTGTACGTCTTGAAGCCAGTAGATACTGTGTCCCTAA nem316_a12.seq

      AGCGTTACCATAAGAAATGCAAATGATCATCAAA                 Majority
               14110     14120     14130
13967 AGCGTTACCATAAGAAATGCAAATGATCATCAAA                 2603_a12.seq
13967 AGCGTTACCATAAGAAATGCAAATGATCATCAAA                 nem316_a12.seq
```

Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

FIGURE 20U

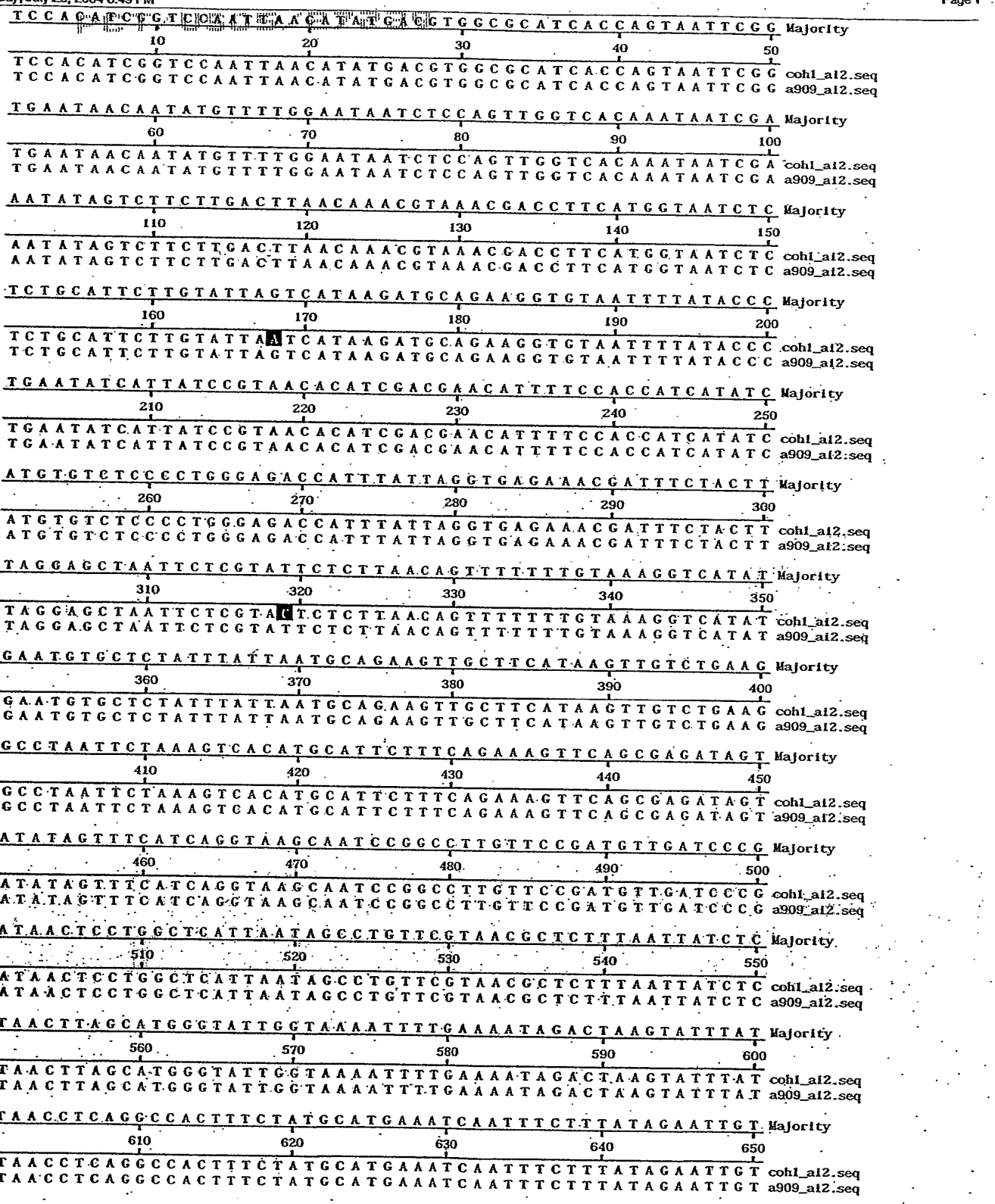
TCCACATCGGTCCAATTAACATATGACGTGGCGCCATCACCAGTAATTCGG Majority
10 20 30 40 50
1 TCCACATCGGTCCAATTAACATATGACGTGGCGCCATCACCAGTAATTCGG cohl_al2.seq
1 TCCACATCGGTCCAATTAACATATGACGTGGCGCCATCACCAGTAATTCGG a909_al2.seq
TGAATAACAATATGTTTTGGAATAATCTCCAGTTGGTCACAAATAATCGA Majority
60 70 80 90 100
51 TGAATAACAATATGTTTTGGAATAATCTCCAGTTGGTCACAAATAATCGA cohl_al2.seq
51 TGAATAACAATATGTTTTGGAATAATCTCCAGTTGGTCACAAATAATCGA a909_al2.seq
AATATAGTCTTCTTGACTTAACAAACGTAAACGACCTTCATGGTAATCTC Majority
110 120 130 140 150
101 AATATAGTCTTCTTGACTTAACAAACGTAAACGACCTTCATGGTAATCTC cohl_al2.seq
101 AATATAGTCTTCTTGACTTAACAAACGTAAACGACCTTCATGGTAATCTC a909_al2.seq
TCTGCATTCTTGTATTAGTCATAAGATGCAGAAGGTGTAATTTTATACCC Majority
160 170 180 190 200
151 TCTGCATTCTTGTATTAATCATAAGATGCAGAAGGTGTAATTTTATACCC cohl_al2.seq
151 TCTGCATTCTTGTATTAGTCATAAGATGCAGAAGGTGTAATTTTATACCC a909_al2.seq
TGAATATCATTATCCGTAACACATCGACGAACATTTTCCACCATCATATC Majority
210 220 230 240 250
201 TGAATATCATTATCCGTAACACATCGACGAACATTTTCCACCATCATATC cohl_al2.seq
201 TGAATATCATTATCCGTAACACATCGACGAACATTTTCCACCATCATATC a909_al2.seq
ATGTGTCTCCCCTGGGAGACCATTTATTAGGTGAGAAACGATTTCTACTT Majority
260 270 280 290 300
251 ATGTGTCTCCCCTGGGAGACCATTTATTAGGTGAGAAACGATTTCTACTT cohl_al2.seq
251 ATGTGTCTCCCCTGGGAGACCATTTATTAGGTGAGAAACGATTTCTACTT a909_al2.seq
TAGGAGCTAATTCTCGTATTCTCTTAACAGTTTTTTTGTAAAGGTCATAT Majority
310 320 330 340 350
301 TAGGAGCTAATTCTCGTACTCTCTTAACAGTTTTTTTGTAAAGGTCATAT cohl_al2.seq
301 TAGGAGCTAATTCTCGTATTCTCTTAACAGTTTTTTTGTAAAGGTCATAT a909_al2.seq
GAATGTGCTCTATTTATTAATGCAGAAGTTGCTTCATAAGTTGTCTGAAG Majority
360 370 380 390 400
351 GAATGTGCTCTATTTATTAATGCAGAAGTTGCTTCATAAGTTGTCTGAAG cohl_al2.seq
351 GAATGTGCTCTATTTATTAATGCAGAAGTTGCTTCATAAGTTGTCTGAAG a909_al2.seq
GCCTAATTCTAAAGTCACATGCATTCTTTCAGAAAGTTCAGCGAGATAGT Majority
410 420 430 440 450
401 GCCTAATTCTAAAGTCACATGCATTCTTTCAGAAAGTTCAGCGAGATAGT cohl_al2.seq
401 GCCTAATTCTAAAGTCACATGCATTCTTTCAGAAAGTTCAGCGAGATAGT a909_al2.seq
ATATAGTTTCATCAGGTAAGCAATCCGGCCTTGTTCCGATGTTGATCCCG Majority
460 470 480 490 500
451 ATATAGTTTCATCAGGTAAGCAATCCGGCCTTGTTCCGATGTTGATCCCG cohl_al2.seq
451 ATATAGTTTCATCAGGTAAGCAATCCGGCCTTGTTCCGATGTTGATCCCG a909_al2.seq
ATAACTCCTGGCTCATTAATAGCCTGTTCGTAACGCTCTTTAATTATCTC Majority
510 520 530 540 550
501 ATAACTCCTGGCTCATTAATAGCCTGTTCGTAACGCTCTTTAATTATCTC cohl_al2.seq
501 ATAACTCCTGGCTCATTAATAGCCTGTTCGTAACGCTCTTTAATTATCTC a909_al2.seq
TAACTTAGCATGGGTATTGGTAAAATTTTGAAAATAGACTAAGTATTTAT Majority
560 570 580 590 600
551 TAACTTAGCATGGGTATTGGTAAAATTTTGAAAATAGACTAAGTATTTAT cohl_al2.seq
551 TAACTTAGCATGGGTATTGGTAAAATTTTGAAAATAGACTAAGTATTTAT a909_al2.seq
TAACCTCAGGCCACTTTCTATGCATGAAATCAATTTCTTTATAGAATTGT Majority
610 620 630 640 650
601 TAACCTCAGGCCACTTTCTATGCATGAAATCAATTTCTTTATAGAATTGT cohl_al2.seq
601 TAACCTCAGGCCACTTTCTATGCATGAAATCAATTTCTTTATAGAATTGT a909_al2.seq

Figure 21

```
TCACGAATAGGAGCTTCTGGAGCAACTATAGCATCCCCTGAACCAGAAAC Majority
          660       670       680       690       700
651 TCACGAATAGGAGCTTCTGGAGCAACTATAGCATCCCCTGAACCAGAAAC cohl_al2.seq
651 TCACGAATAGGAGCTTCTGGAGCAACTATAGCATCCCCTGAACCAGAAAC a909_al2.seq

TGTGCAAAAAGTGCACCCTCCTCTAGCAACTGTTCCATCTCTGTTAGGAC Majority
          710       720       730       740       750
701 TGTGCAAAAAGTGCACCCTCCTCTAGCAACTGTTCCATCTCTGTTAGGAC cohl_al2.seq
701 TGTGCAAAAAGTGCACCCTCCTCTAGCAACTGTTCCATCTCTGTTAGGAC a909_al2.seq

AGTCAAAACCAGCATCTATAGGTAATTTAAATATTTTTTCTCCAAAGAGT Majority
          760       770       780       790       800
751 AGTCAAAACCAGCATCTATAGGTAATTTAAATATTTTTTCTCCAAAGAGT cohl_al2.seq
751 AGTCAAAACCAGCATCTATAGGTAATTTAAATATTTTTTCTCCAAAGAGT a909_al2.seq

TCTCGATAATAATCATTAATCGCACGATAACGTTTTTTTCATAGGATAATT Majority
          810       820       830       840       850
801 TCTCGATAATAATCATTAATCGCACGATAACGTTTTTTTCATAGGATAATT cohl_al2.seq
801 TCTCGATAATAATCATTAATCGCACGATAACGTTTTTTTCATAGGATAATT a909_al2.seq

GTATCACAATTTTAACTAAAATAACCTCACTACTACAATAAAACTAAAAA Majority
          860       870       880       890       900
851 GTATCACAATTTTAACTAAAATAACCTCACTACTACAATAAAACTAAAAA cohl_al2.seq
851 GTATCACAATTTTAACTAAAATAACCTCACTACTACAATAAAACTAAAAA a909_al2.seq

AGATTGGAACGTCAGTTAGTTCCAATCTTTTATTTACTTCACTTTCTTTA Majority
          910       920       930       940       950
901 AGATTGGAACGTCAGTTAGTCCCAATCTTTTATTTACTTCACTTTCTTTA cohl_al2.seq
901 AGATTGGAACGTCAGTTAGTTCCAATCTTTTATTTACTTCACTTTCTTTA a909_al2.seq

ACCAATCCTTGGCTAAAAAGATATACGCAGTTAGATTCAAAATACCATAA Majority
          960       970       980       990      1000
951 ACCAATCCTTGGATAAAAAGATATACGCAGTTAGATTCAAAATACCATAA cohl_al2.seq
951 ACCAATCCTTGGCTAAAAAGATATACGCAGTTAGATTCAAAATACCATAA a909_al2.seq

GCAAGTATAAAACCAGCTAAAACATCTGTCGGAAAATGAACCCCTAGGTA Majority
         1010      1020      1030      1040      1050
1001 GCAAGTATAAAACCAGCTAAAACATCTGTCGGAAAATGAACCCCTAGGTA cohl_al2.seq
1001 GCAAGTATAAAACCAGCTAAAACATCTGTCGGAAAATGAACCCCTAGGTA a909_al2.seq

AATACGAGATAACCCAATTAAAAAAATGAGCAAACCCAATGTACCTTGGC Majority
         1060      1070      1080      1090      1100
1051 AATACGAGATAACCCAATTAAAAAAATGAGCAAACCCAATGTACCTTGGC cohl_al2.seq
1051 AATACGAGATAACCCAATTAAAAAAATGAGCAAACCCAAAATACCTTGGC a909_al2.seq

ACAACAGTTTCCATATACTCTTAGGCATATAGTACTGCAATAAAATAATA Majority
         1110      1120      1130      1140      1150
1101 ACAACAGTTTCCATATACTCTTAGGCATATAGTACTGCAATAAAATAATA cohl_al2.seq
1101 ACAACAGTTTCCATATACTCTTAGGCATATAGTACTGCAATAAAATAATA a909_al2.seq

CTACTCCCAAATATCATAAATGTTCCCATCGAGTGCCCACTGGGAAACGA Majority
         1160      1170      1180      1190      1200
1151 CTACTCCCAAATATCATAAATGTTCCCATCGAGTGCCCACTGGGAAACGA cohl_al2.seq
1151 ATACTCCCAAATATCATAAATGTTCCCATCGAGTGCCCACTGGGAAACGA a909_al2.seq

ATAGCCACCTGCAAATACTAAATGGGTTAAAGTTGGTCTCACTCTTTGAA Majority
         1210      1220      1230      1240      1250
1201 ATAGCCACCTGCAAATACTAAATGGGTTAAAGTTGGTCTCACTCTTTGAA cohl_al2.seq
1201 ATAGCCACCTGCAAATACTAAATGGGTTAAAGTTGGTCTCACTCTTTGAA a909_al2.seq

AAATAAGTTTTAAAGAAAGTATACATATACCAGAGATAATAGCATTTACT Majority
         1260      1270      1280      1290      1300
1251 AAATAAGTTTTAAAGAAAGTATACATATACCAGAGATAATAGCATTTACT cohl_al2.seq
1251 AAATAAGTTTTAAAGAAAGTATACATATACCAGAGATAATAGCATTTACT a909_al2.seq
```

FIGURE 21A

```
GCGATAAATCTAGCTTGAGGATACCACTTCTTAAGGTAACAGAAAGTGAC Majority
        1310        1320        1330        1340        1350
1301 GCGATAAATCTAGCTTGAGGATACCACTTCTTAAGGTAACAGAAAGTGAC cohl_a12.seq
1301 GCGATAAATCTAGCTTGAGGATACCACTTCTTAAGGTAACAGAAAGTGAC a909_a12.seq

GCTCATAATCGCAATAGCTATCTGGCTTACAGTATTACCAACCACAGTGA Majority
        1360        1370        1380        1390        1400
1351 GCTCATAATCGCAATAGCTATCTGGCTTACAGTATTACCAACCACAGTGA cohl_a12.seq
1351 GCTCATAATCGCAATAGCTATCTGGCTTACAGTATTACCAACCACAGTGA a909_a12.seq

TTAACTTGAAAAATCTTGTAGAAAGATTTGGCAACTGTCCTCTAACACTT Majority
        1410        1420        1430        1440        1450
1401 TTAACTTAAAAAATCTTGTAGAAAGATTTGGCAACTGTCCTCTAACACTT cohl_a12.seq
1401 TTAACTTGAAAAATCTTGTAGAAAGATTTGGCAACTGTCCTCTAACACTT a909_a12.seq

TCTTGAATAGTTTGGTCAAATGCGATTACAGTGTCGGGCCAATATTTGAT Majority
        1460        1470        1480        1490        1500
1451 TCTTGAATAGTTTGGTCAAATGCGATTACAGTGTCGGGCCAATATTTGAT cohl_a12.seq
1451 TCTTGAATAGTTTGGTCAAATGCGATTACAGTGTCGGGCCAATATTTGAT a909_a12.seq

GACCAATCCTAAACTGAAAAATAAGATAATAGCAATAAATGCTTGAATAA Majority
        1510        1520        1530        1540        1550
1501 GACCAATCCTAAACTGAAAAATAAGATAATAGCAATAAATGCTTGAATAA cohl_a12.seq
1501 GACCAATCCTAAACTGAAAAATAAGATAATAGCAATAAATGCTTGAATAA a909_a12.seq

GTTTACTATTTTGACGAGATAAGATTAGTCTTTTTATATCTTTCTAATAT Majority
        1560        1570        1580        1590        1600
1551 GTTTACTATTTTGACGAGATAACATTAGTCTTTTTATATCTTTCTAATAT cohl_a12.seq
1551 GTTTACTATTTTGACGAGATAACATTAGTCTTTTTATATCTTTCTAATAT a909_a12.seq

TGGCAAACAAGCCACGTAAGTTAGATAGAAAACAATCGAAATTAAAATTC Majority
        1610        1620        1630        1640        1650
1601 TGGCAAACAAGCCACGTAAGTTAGATAGAAAACAATCGAAATTAAAATTC cohl_a12.seq
1601 TGGCAAACAAGCCACGTAAGTTAGATAGAAAACAATCGAAATTAAAATTC a909_a12.seq

CCTCAACGATATTAAATGGAATAACCATTGTTAAAAGGTAATTGCCTACA Majority
        1660        1670        1680        1690        1700
1651 CCTCAACGATATTAAATGGAATAACCATTGTTAAAAGGTAATTGCCTACA cohl_a12.seq
1651 CCTCAACGATATTAAATGGAATAACCATTGTTAAAAGGTAATTGCCTACA a909_a12.seq

CCAATAAATGTTCTGATATCAAAGTTAGCAAATATAGCATACAAAGGAAT Majority
        1710        1720        1730        1740        1750
1701 CCAATAAATGTTCTGATATCAAAGTTAGCAAATATAGCATACAAAGGAAT cohl_a12.seq
1701 CCAATAAATGTTCTGATATCAAAGTTAGCAAATATAGCATACAAAGGAAT a909_a12.seq

CGCAAAGACATAGTTGAGAGCTACCATAGATACAGTCAAGCTAACTGTAC Majority
        1760        1770        1780        1790        1800
1751 CGCAAAGACATAGTTGAGAGCTACCATAGATACAGTCAAGCTAACTGTAC cohl_a12.seq
1751 CGCAAAGACATAGTTGAGAGCTACCATAGATACAGTCAAGCTAACTGTAC a909_a12.seq

CAAATAAACTAGCTTTAATAAAATCTTTTGCACTCTCTCTATTTTTCCAG Majority
        1810        1820        1830        1840        1850
1801 CAAATAAACTAGCTTTAATAAAATCTTTTGCACTCTCTCTATTTTTCCAG cohl_a12.seq
1801 CAAATAAACTAGCTTTAATAAAATCTTTTGCACTCTCTCTATTTTTCCAG a909_a12.seq

AAAATAGCGAAACTTGCTAAAAATAGAGCTAGAGCAACCATATTCATCGG Majority
        1860        1870        1880        1890        1900
1851 AAAATAGCGAAACTTGCTAAAAATAGAGCTAGAGCAACCATATTCATCGG cohl_a12.seq
1851 AAAATAGCGAAACTTGCTAAAAATAGAGCTAGAGCAACCATATTCATCGG a909_a12.seq

TAAACCGATAAAGGTTTCTGGACCACGATTAGCAAGTATAACTTTTAAAA Majority
        1910        1920        1930        1940        1950
1901 TAAACCGATAAAGGTTTCTGGACCACGATTAGCAAGTATAACTTTTAAAA cohl_a12.seq
1901 TAAACCGATAAAGGTTTCTGGACCACGATTAGCAAGTATAACTTTTAAAA a909_a12.seq
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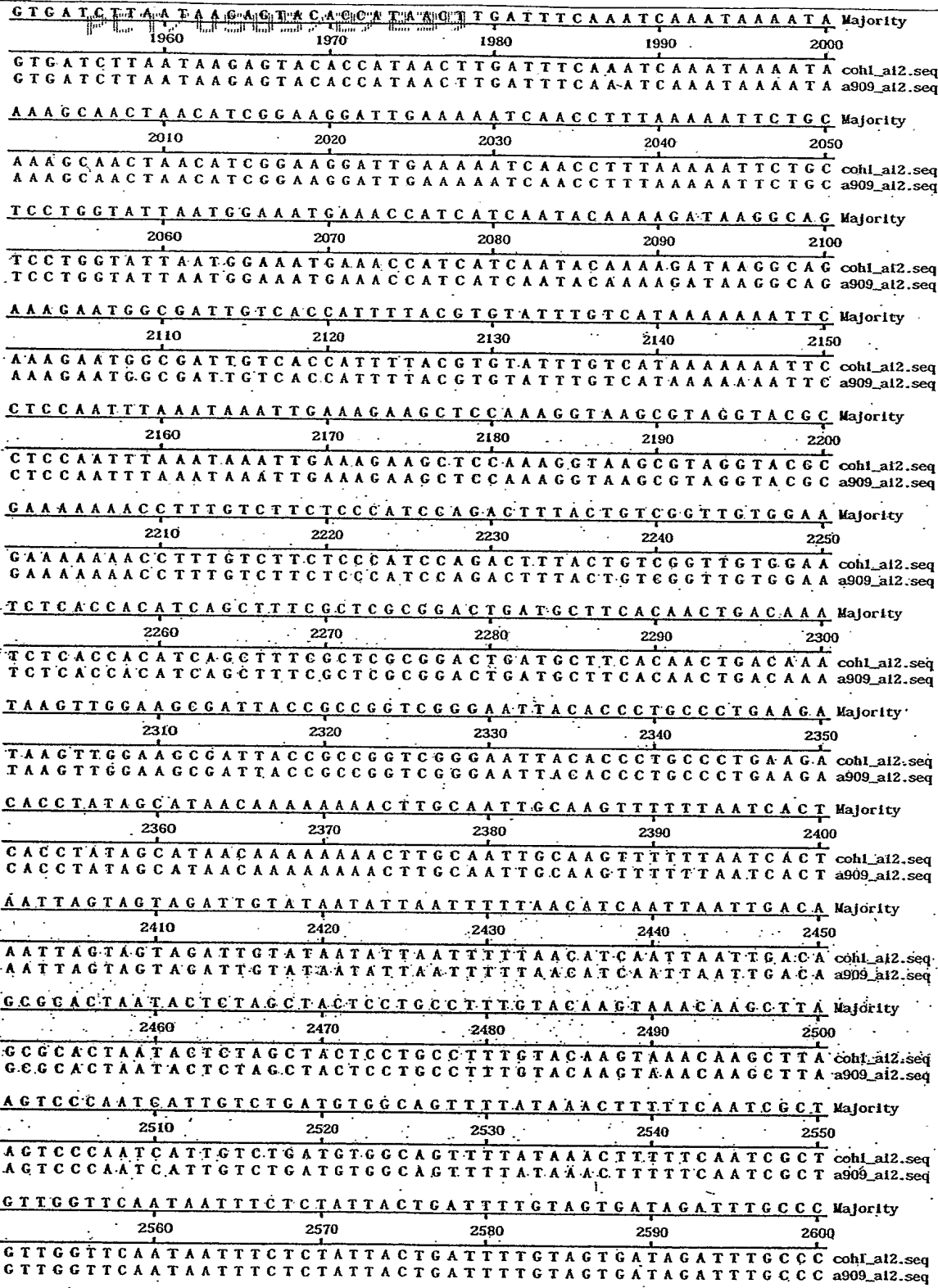
FIGURE 21B


GTGATCTTAATAAGAGTACACCATAACTTGATTTCAAATCAAATAAAATA Majority
1960 1970 1980 1990 2000
1951 GTGATCTTAATAAGAGTACACCATAACTTGATTTCAAATCAAATAAAATA cohl_al2.seq
1951 GTGATCTTAATAAGAGTACACCATAACTTGATTTCAAATCAAATAAAATA a909_al2.seq
AAAGCAACTAACATCGGAAGGATTGAAAAATCAACCTTTAAAAATTCTGC Majority
2010 2020 2030 2040 2050
2001 AAAGCAACTAACATCGGAAGGATTGAAAAATCAACCTTTAAAAATTCTGC cohl_al2.seq
2001 AAAGCAACTAACATCGGAAGGATTGAAAAATCAACCTTTAAAAATTCTGC a909_al2.seq
TCCTGGTATTAATGGAAATGAAACCATCATCAATACAAAAGATAAGGCAG Majority
2060 2070 2080 2090 2100
2051 TCCTGGTATTAATGGAAATGAAACCATCATCAATACAAAAGATAAGGCAG cohl_al2.seq
2051 TCCTGGTATTAATGGAAATGAAACCATCATCAATACAAAAGATAAGGCAG a909_al2.seq
AAAGAATGGCGATTGTCACCATTTTACGTGTATTTGTCATAAAAAAAATTC Majority
2110 2120 2130 2140 2150
2101 AAAGAATGGCGATTGTCACCATTTTACGTGTATTTGTCATAAAAAAAATTC cohl_al2.seq
2101 AAAGAATGGCGATTGTCACCATTTTACGTGTATTTGTCATAAAAAAAATTC a909_al2.seq
CTCCAATTTAAATAAATTGAAAGAAGCTCCAAAGGTAAGCGTAGGTACGC Majority
2160 2170 2180 2190 2200
2151 CTCCAATTTAAATAAATTGAAAGAAGCTCCAAAGGTAAGCGTAGGTACGC cohl_al2.seq
2151 CTCCAATTTAAATAAATTGAAAGAAGCTCCAAAGGTAAGCGTAGGTACGC a909_al2.seq
GAAAAAAAACCTTTGTCTTCTCCCATCCAGACTTTACTGTCGGTTGTGGAA Majority
2210 2220 2230 2240 2250
2201 GAAAAAAAACCTTTGTCTTCTCCCATCCAGACTTTACTGTCGGTTGTGGAA cohl_al2.seq
2201 GAAAAAAAACCTTTGTCTTCTCCCATCCAGACTTTACTGTCGGTTGTGGAA a909_al2.seq
TCTCACCACATCAGCTTTCGCTCGCGGACTGATGCTTCACAACTGACAAA Majority
2260 2270 2280 2290 2300
2251 TCTCACCACATCAGCTTTCGCTCGCGGACTGATGCTTCACAACTGACAAA cohl_al2.seq
2251 TCTCACCACATCAGCTTTCGCTCGCGGACTGATGCTTCACAACTGACAAA a909_al2.seq
TAAGTTGGAAGCGATTACCGCCGGTCGGGAATTACACCCTGCCCTGAAGA Majority
2310 2320 2330 2340 2350
2301 TAAGTTGGAAGCGATTACCGCCGGTCGGGAATTACACCCTGCCCTGAAGA cohl_al2.seq
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CACCTATAGCATAACAAAAAAAAACTTGCAATTGCAAGTTTTTTAATCACT Majority
2360 2370 2380 2390 2400
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2401 AATTAGTAGTAGATTGTATAATATTAATTTTTAACATCAATTAATTGACA cohl_al2.seq
2401 AATTAGTAGTAGATTGTATAATATTAATTTTTAACATCAATTAATTGACA a909_al2.seq
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2451 GCGCACTAATACTCTAGCTACTCCTGCCTTTGTACAAGTAAACAAGCTTA cohl_al2.seq
2451 GCGCACTAATACTCTAGCTACTCCTGCCTTTGTACAAGTAAACAAGCTTA a909_al2.seq
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2501 AGTCCCAATCATTGTCTGATGTGGCAGTTTTATAAACTTTTTCAATCGCT a909_al2.seq
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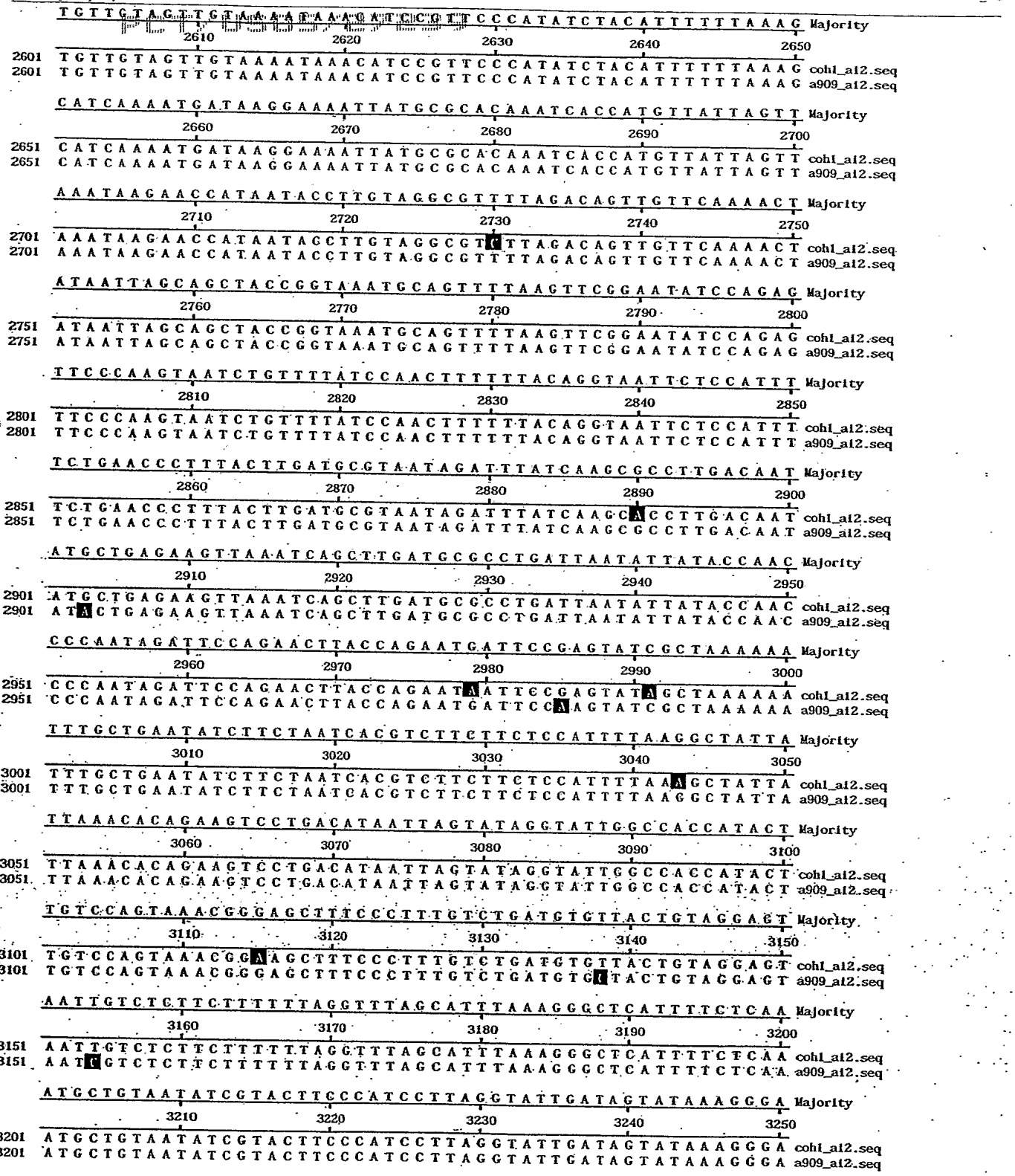
FIGURE 21C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2601 TGTTGTAGTTGTAAAATAAACATCCGTTCCCATATCTACATTTTTTAAAG a909_al2.seq
CATCAAAATGATAAGGAAAATTATGCGCACAAATCACCATGTTATTAGTT Majority
2660 2670 2680 2690 2700
2651 CATCAAAATGATAAGGAAAATTATGCGCACAAATCACCATGTTATTAGTT cohl_al2.seq
2651 CATCAAAATGATAAGGAAAATTATGCGCACAAATCACCATGTTATTAGTT a909_al2.seq
AAATAAGAACCATAATACCTTGTAGGCGTTTTAGACAGTTGTTCAAAACT Majority
2710 2720 2730 2740 2750
2701 AAATAAGAACCATAATAGCTTGTAGGCGTCTTAGACAGTTGTTCAAAACT cohl_al2.seq
2701 AAATAAGAACCATAATACCTTGTAGGCGTTTTAGACAGTTGTTCAAAACT a909_al2.seq
ATAATTAGCAGCTACCGGTAAATGCAGTTTTAAGTTCGGAATATCCAGAG Majority
2760 2770 2780 2790 2800
2751 ATAATTAGCAGCTACCGGTAAATGCAGTTTTAAGTTCGGAATATCCAGAG cohl_al2.seq
2751 ATAATTAGCAGCTACCGGTAAATGCAGTTTTAAGTTCGGAATATCCAGAG a909_al2.seq
TTCCCAAGTAATCTGTTTTATCCAACTTTTTTACAGGTAATTCTCCATTT Majority
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2801 TTCCCAAGTAATCTGTTTTATCCAACTTTTTTACAGGTAATTCTCCATTT cohl_al2.seq
2801 TTCCCAAGTAATCTGTTTTATCCAACTTTTTTACAGGTAATTCTCCATTT a909_al2.seq
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2860 2870 2880 2890 2900
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2851 TCTGAACCCTTTACTTGATGCGTAATAGATTTATCAAGCGCCTTGACAAT a909_al2.seq
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2910 2920 2930 2940 2950
2901 ATGCTGAGAAGTTAAATCAGCTTGATGCGCCTGATTAATATTATACCAAC cohl_al2.seq
2901 ATACTGAGAAGTTAAATCAGCTTGATGCGCCTGATTAATATTATACCAAC a909_al2.seq
CCCAATAGATTCCAGAACTTACCAGAATGATTCCGAGTATCGCTAAAAAA Majority
2960 2970 2980 2990 3000
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3001 TTTGCTGAATATCTTCTAATCACGTCTTCTTCTCCATTTTAAAGCTATTA cohl_al2.seq
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3051 TTAAACACAGAAGTCCTGACATAATTAGTATAGGTATTGGCCACCATACT cohl_al2.seq
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3110 3120 3130 3140 3150
3101 TGTCCAGTAAACGGAAGCTTTCCCTTTGTCTGATGTGTTACTGTAGGAGT cohl_al2.seq
3101 TGTCCAGTAAACGGGAGCTTTCCCTTTGTCTGATGTGCTACTGTAGGAGT a909_al2.seq
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3160 3170 3180 3190 3200
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3201 ATGCTGTAATATCGTACTTCCCATCCTTAGGTATTGATAGTATAAAGGGA cohl_al2.seq
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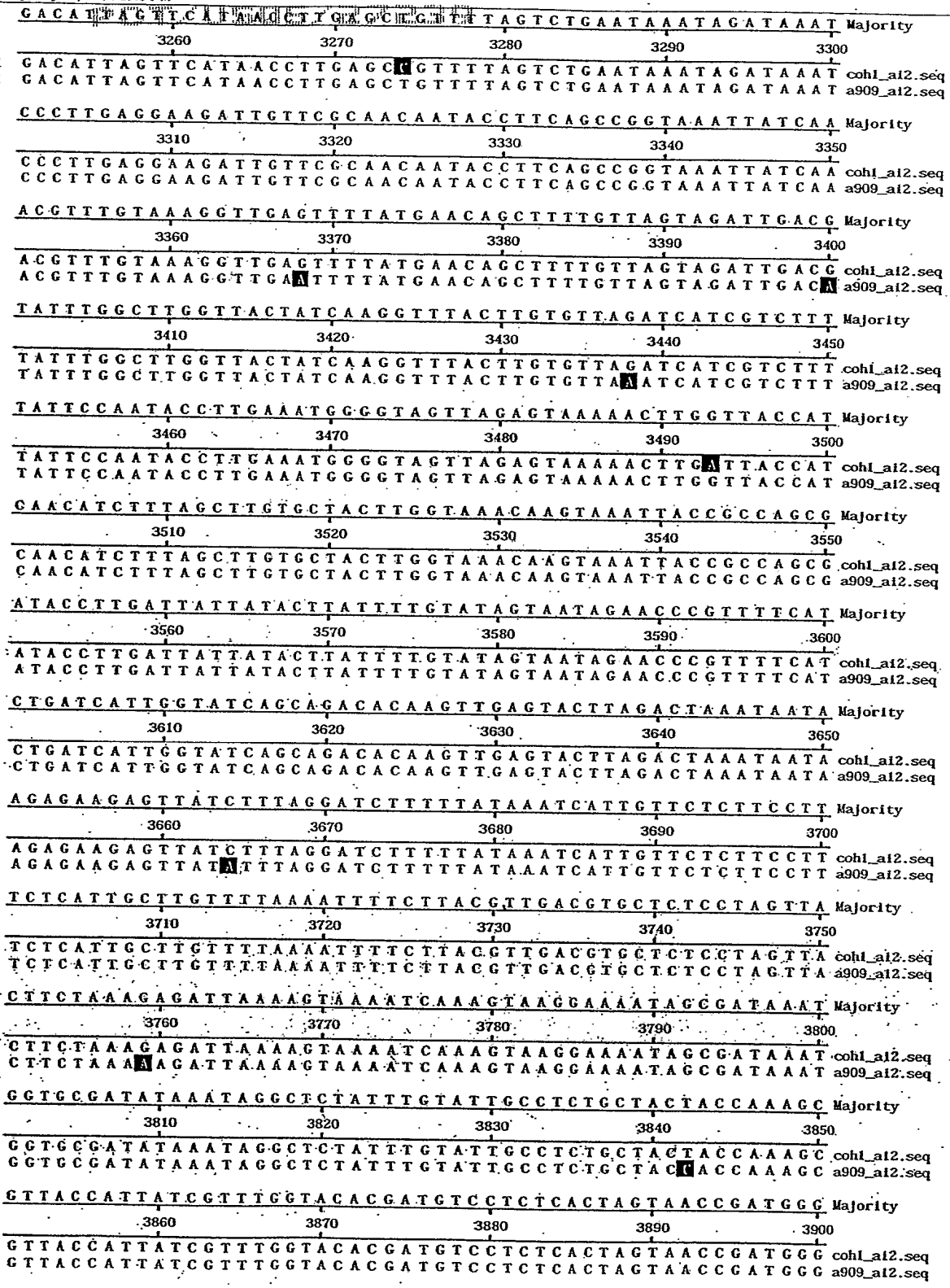
FIGURE 21D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3251 GACATTAGTTCATAACCTTGAGCTGTTTTAGTCTGAATAAATAGATAAAT a909_al2.seq
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ACGTTTGTAAAGGTTGAGTTTTATGAACAGCTTTTGTTAGTAGATTGACG Majority
3360 3370 3380 3390 3400
3351 ACGTTTGTAAAGGTTGAGTTTTATGAACAGCTTTTGTTAGTAGATTGACG cohl_al2.seq
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3401 TATTTGGCTTGGTTACTATCAAGGTTTACTTGTGTTAGATCATCGTCTTT cohl_al2.seq
3401 TATTTGGCTTGGTTACTATCAAGGTTTACTTGTGTTAAATCATCGTCTTT a909_al2.seq
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3460 3470 3480 3490 3500
3451 TATTCCAATACCTTGAAATGGGGTAGTTAGAGTAAAAACTTGATTACCAT cohl_al2.seq
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ATACCTTGATTATTATACTTATTTTGTATAGTAATAGAACCCGTTTTCAT Majority
3560 3570 3580 3590 3600
3551 ATACCTTGATTATTATACTTATTTTGTATAGTAATAGAACCCGTTTTCAT cohl_al2.seq
3551 ATACCTTGATTATTATACTTATTTTGTATAGTAATAGAACCCGTTTTCAT a909_al2.seq
CTGATCATTGGTATCAGCAGACACAAGTTGAGTACTTAGACTAAATAATA Majority
3610 3620 3630 3640 3650
3601 CTGATCATTGGTATCAGCAGACACAAGTTGAGTACTTAGACTAAATAATA cohl_al2.seq
3601 CTGATCATTGGTATCAGCAGACACAAGTTGAGTACTTAGACTAAATAATA a909_al2.seq
AGAGAAGAGTTATCTTTAGGATCTTTTTATAAATCATTGTTCTCTTCCTT Majority
3660 3670 3680 3690 3700
3651 AGAGAAGAGTTATCTTTAGGATCTTTTTATAAATCATTGTTCTCTTCCTT cohl_al2.seq
3651 AGAGAAGAGTTATATTTAGGATCTTTTTATAAATCATTGTTCTCTTCCTT a909_al2.seq
TCTCATTGCTTGTTTTAAAATTTTCTTACGTTGACGTGCTCTCCTAGTTA Majority
3710 3720 3730 3740 3750
3701 TCTCATTGCTTGTTTTAAAATTTTCTTACGTTGACGTGCTCTCCTAGTTA cohl_al2.seq
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CTTCTAAAGAGATTAAAAGTAAAATCAAAGTAAGGAAAATAGCGATAAAT Majority
3760 3770 3780 3790 3800
3751 CTTCTAAAGAGATTAAAAGTAAAATCAAAGTAAGGAAAATAGCGATAAAT cohl_al2.seq
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GGTGCGATATAAATAGGCTCTATTTGTATTGCCTCTGCTACTACCAAAGC Majority
3810 3820 3830 3840 3850
3801 GGTGCGATATAAATAGGCTCTATTTGTATTGCCTCTGCTACTACCAAAGC cohl_al2.seq
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GTTACCATTATCGTTTGGTACACGATGTCCTCTCACTAGTAACCGATGGG Majority
3860 3870 3880 3890 3900
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FIGURE 21E


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3901 TATTAACGCCATATGGTGTACACGTCACCAAAGTTTGGTAGTCTTTACCT cohl_al2.seq
3901 TATTAACACCATATGGTGTACACGTCACCAAAGTTTGGTAGTCTTTACCT a909_al2.seq
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3960 3970 3980 3990 4000
3951 TTAACAATTTGTAAATCCCTCAAATCATCCGGTTTAACTGTTCTGATTTC cohl_al2.seq
3951 TTAACAATTTGTAAATCCCTCAAATCATCCGGTTTAACTGTTCTGATTTG a909_al2.seq
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4010 4020 4030 4040 4050
4001 ATCCACTTGATAAGTATATGTTTCATTTAAGATACTGACTGTCCAGTGGT cohl_al2.seq
4001 ATCCACTTGATAAGTATATGTTTCATTTAAGATACTGACTGTCCAGTGGT a909_al2.seq
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4060 4070 4080 4090 4100
4051 CTCCAACTTTTAACTTATCCAAATCAGAAAAAAGCCTTGAAGAGGGTAAA cohl_al2.seq
4051 CTCCAGCTTTTAACTTATCCAAATCAGAAAAAAGCCTTGAAGAGGGTAAA a909_al2.seq
CCTCTATGTCCTGATAAAATAGAATGAGTTGAGTCTCCTCCAATTGGAAG Majority
4110 4120 4130 4140 4150
4101 CCTCTATGTCCTGATAAAATAGAATGAGTTGAGTCTCCTCCAATTGGAAG cohl_al2.seq
4101 CCTCTATGTCCTGATAAAATAGAATGAGTTGAGTCTCCTCCAATTGGAAG a909_al2.seq
ACTACTTCCTTCTAAATGACCAATAGAAGTTTGAAGCACTTTTTCACTTG Majority
4160 4170 4180 4190 4200
4151 ACTACTTCCTTCTAAATGACCAATAGAAGTTTGAAGCACTTTTTCACTTG cohl_al2.seq
4151 ACTACTTCCTTCTAAATGACCAATAGAAGTTTGAAGCACCTTTTTCACTTG a909_al2.seq
TACCATGATAAAGTGGTAATTTTATGTTTATCTTTGGAATTGAAATATAA Majority
4210 4220 4230 4240 4250
4201 TACCATGATAAAGTGGTAATTTTATGTTTATCTTTGGAATTGAAATATAA cohl_al2.seq
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4260 4270 4280 4290 4300
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CTCTTGGTTAGTCATGTGCCACTTCATTCCTGAAGTTTTAAATTGCTTAT Majority
4310 4320 4330 4340 4350
4301 CTCTTGGCTAGTCATGTGCCACTTCATTCCTGAAGTTTTAAATTGCTTAT cohl_al2.seq
4301 CTCTTGGTCAGTCATGTGCCACTTCATTCCTGAAGTTTTAAATTGCTTAT a909_al2.seq
TATATTCTTTGGCTCGGTTAATAATTTTTTTATAGTCGTTTTCATCCATA Majority
4360 4370 4380 4390 4400
4351 TATATTCTTTGGCTCGGTTAATAATTTTTTTATAATCGTTTTCATCCATA cohl_al2.seq
4351 TATATTCTTTGGCTCGGTTAATAATTTTTTTATAGTCGTTTTCATCCATA a909_al2.seq
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4410 4420 4430 4440 4450
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ATTCCAATAATTAGCAAGTGAAGGATAAGCCATTAAGCCTACCCCCACTG Majority
4460 4470 4480 4490 4500
4451 ATTCCAATAATTAGCAAGTGAAGGATAAGCCATTAAGCCTACCCCCACTG cohl_al2.seq
4451 ATTCCAATAATTAGCAAGTGAAGGATAAGCCATTAAGCCTACCCCCACTG a909_al2.seq
CAATTATAGTGACAAGCAAAATGGATACTAAATGTTGTCTTATTTTTTTC Majority
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4501 CAATTATAGTGACAAGCAAAATGGATACTAAATGTTGTCTTATTTTTTTC cohl_al2.seq
4501 CAATTATAGTGACAAGCAAAATGGATACTAAATGTTGTCTTATTTTTTTC a909_al2.seq

FIGURE 21F

```
     ATATATTTTAAATCTGTACCACTTTGCTAGCCCATCTTATTAAGAACGTA Majority
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4551 ATATATTTTAAATCTGTACCACTTTGCTAGCCCATCTTATTAAGAACGTA a909_a12.seq

     AACGACGACGAGCAACAAGCACGATACCTGCTCCTATTACTAAAATTGCA Majority
              4610      4620      4630      4640      4650
4601 AACGACGACGAGCAACAAGCACGATACCTGCTCCTATTACTAAAATTGCA coh1_a12.seq
4601 AACGACGACGAGCAACAAGCACGATACCTGCTCCTATTACTAAAATTGCA a909_a12.seq

     CCTATAATGTAGAAAATTGTTGTACCAATACCACCTGTTGAAGGCAACTC Majority
              4660      4670      4680      4690      4700
4651 CCTATAATGTAGAAAATTGTTGTACCAATACCACCTGTTGAAGGCAACTC coh1_a12.seq
4651 CCTATAATGTAGAAAATTGTTGTACCAATACCACCTGTTGAAGGCAACTC a909_a12.seq

     AGTACCTTTGTTATTTTCAACAGTTGGGTTAACTAAAAGGTTATCTGAAT Majority
              4710      4720      4730      4740      4750
4701 AGTACCTTTGTTATTTTCAACAGTTGGGTTAACTAAAAGGTTATCTGAAT coh1_a12.seq
4701 AGTACCTTTGTTATTTTCAACAGTTGGGTTAACTAAAAGGTTATCTGAAT a909_a12.seq

     TAGTCGTATCAGTGGCTCCATCTCCTAAAATAACCTTCTGAGAGTTATCT Majority
              4760      4770      4780      4790      4800
4751 TAGTCGTATCAGTGGCTCCATCTCCTAAAATAACCTTCTGAGAGTTATCT coh1_a12.seq
4751 TAGTCGTATCAGTGGCTCCATCTCCTAAAATAACCTTCTGAGAGTTATCT a909_a12.seq

     AACAAATTGTAACCTAAGGGAGCCTTTTTCTCAACTAGATAGTATGTACC Majority
              4810      4820      4830      4840      4850
4801 AACAAATTGTAACCTAAGGGAGCCTTTTTCTCAACTAGATAGTATGTACC coh1_a12.seq
4801 AACAAATTGTAACCTAAGGGAGCCTTTTTCTCAACTAGATAGTATGTACC a909_a12.seq

     TTCTTTCAAGCCTGTAATGGTAATTATACCATCTGCTCCTGTTGTATATT Majority
              4860      4870      4880      4890      4900
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     CTGTTGCATTAGCTTCTGTGCCCCATTCAACGTTATTTGTATCGTTAAAG Majority
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     TTTAGAAATTGACCCGTAGCATTCTTTAAAACAAATATAGCACCTTGTAA Majority
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4951 TTTAGAAATTGACCCGTAGCATTCTTTAAAACAAATATAGCACCTTGTAA a909_a12.seq

     TGAAGCTTTTGTGGAACCATCAATTTTTTTTATAGTAATTTGACCATCCC Majority
              5010      5020      5030      5040      5050
5001 TGAAGCTTTTGTGGAACCATCAATTTTTTTTATAGTAATTTGACCATCCC coh1_a12.seq
5001 TGAAGCTTTTGTGGAACCATCAATTTTTTTTATAGTAATTTGACCATCCC a909_a12.seq

     TCACTGTTACTTTTTGACCTGGGTCATCATTGCTAGTATTGGGGTTGATG Majority
              5060      5070      5080      5090      5100
5051 TCACTGTTACTTTTTGACCTGGGTCATCATTGCTAGTATTGGGGTTGATG coh1_a12.seq
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     GTCGCAATGTTTGTATTTTCTGGTAAATCAGCTGAACCTGGTTTAGCTCC Majority
              5110      5120      5130      5140      5150
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     ACTCTTTAATACTCCTGTATAAGTGACTGTGATTGTATTTATTCCCTTAT Majority
              5160      5170      5180      5190      5200
5151 ACTCTTTAATACTCCTGTATAAGTGACTGTGATTGTATTTATTCCCTTAT coh1_a12.seq
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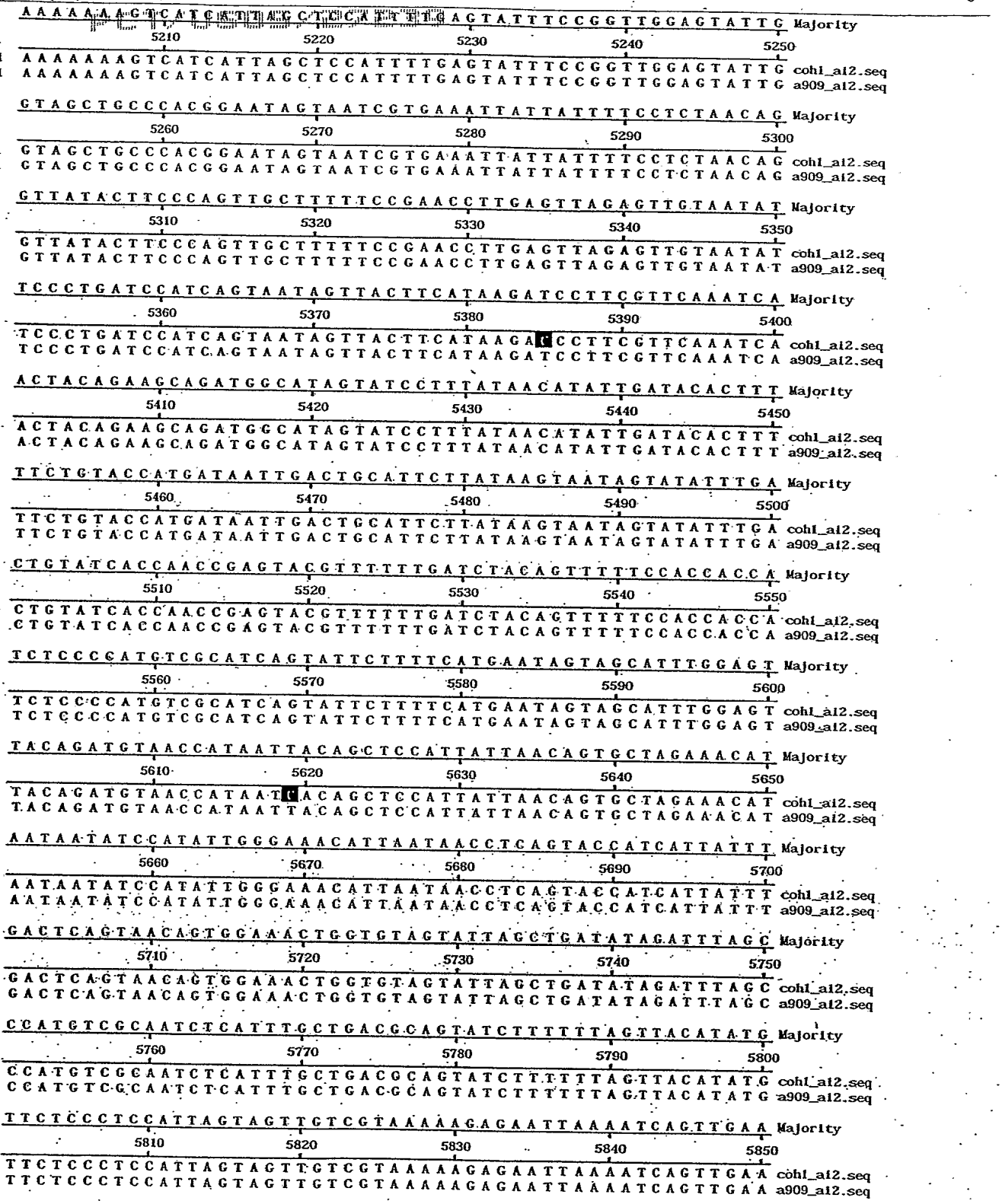
FIGURE 21G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GTAGCTGCCCACGGAATAGTAATCGTGAAATTATTATTTTCCTCTAACAG Majority
5260 5270 5280 5290 5300
5251 GTAGCTGCCCACGGAATAGTAATCGTGAAATTATTATTTTCCTCTAACAG cohl_al2.seq
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GTTATACTTCCCAGTTGCTTTTTCCGAACCTTGAGTTAGAGTTGTAATAT Majority
5310 5320 5330 5340 5350
5301 GTTATACTTCCCAGTTGCTTTTTCCGAACCTTGAGTTAGAGTTGTAATAT cohl_al2.seq
5301 GTTATACTTCCCAGTTGCTTTTTCCGAACCTTGAGTTAGAGTTGTAATAT a909_al2.seq
TCCCTGATCCATCAGTAATAGTTACTTCATAAGATCCTTCGTTCAAATCA Majority
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5460 5470 5480 5490 5500
5451 TTCTGTACCATGATAATTGACTGCATTCTTATAAGTAATAGTATATTTGA cohl_al2.seq
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5560 5570 5580 5590 5600
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5610 5620 5630 5640 5650
5601 TACAGATGTAACCATAATCACAGCTCCATTATTAACAGTGCTAGAAACAT cohl_al2.seq
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5660 5670 5680 5690 5700
5651 AATAATATCCATATTGGGAAACATTAATAACCTCAGTACCATCATTATTT cohl_al2.seq
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5710 5720 5730 5740 5750
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5760 5770 5780 5790 5800
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5810 5820 5830 5840 5850
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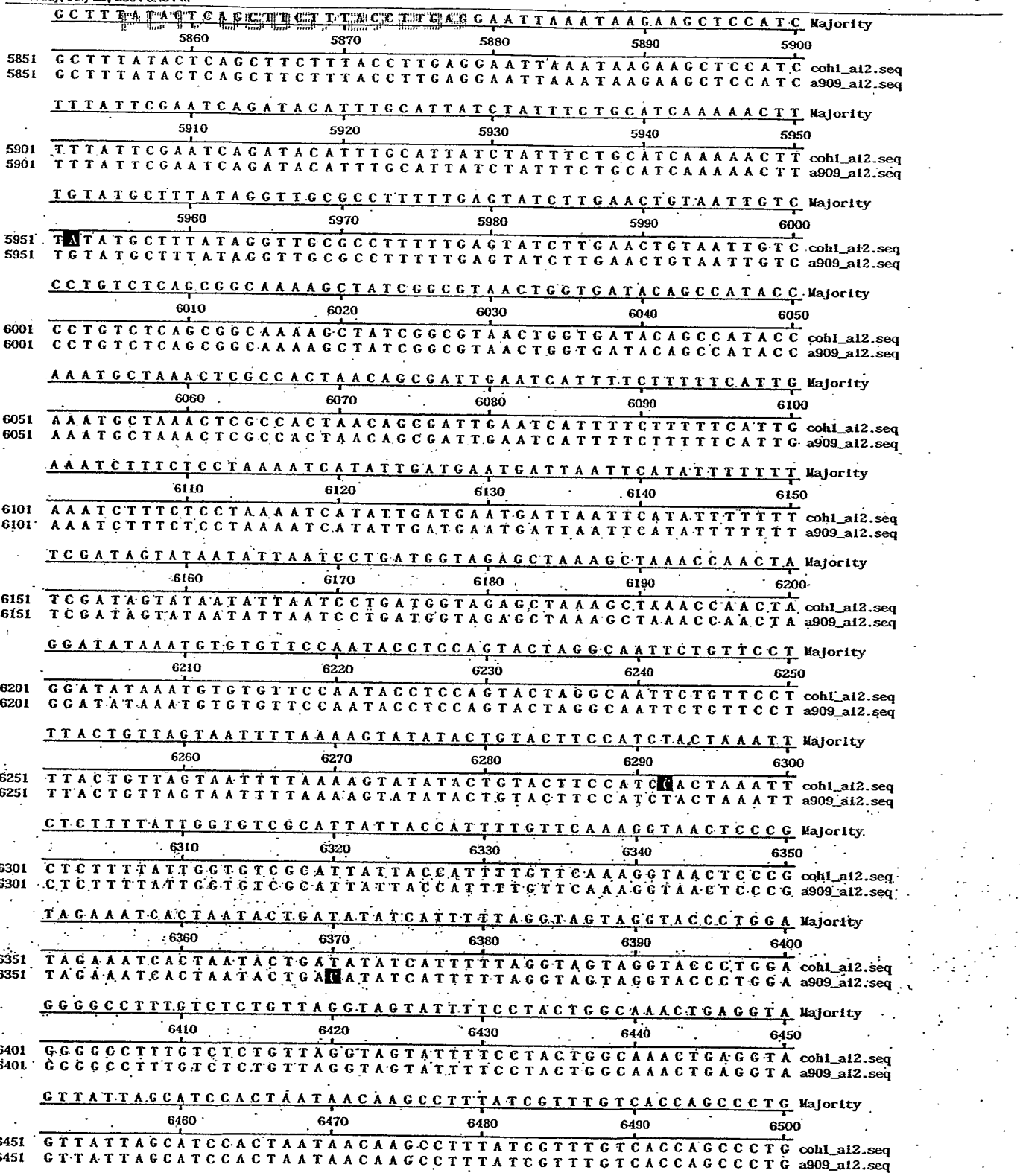
FIGURE 21H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5860 5870 5880 5890 5900
5851 GCTTTATACTCAGCTTCTTTACCTTGAGGAATTAAATAAGAAGCTCCATC cohl_al2.seq
5851 GCTTTATACTCAGCTTCTTTACCTTGAGGAATTAAATAAGAAGCTCCATC a909_al2.seq
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5910 5920 5930 5940 5950
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FIGURE 21I

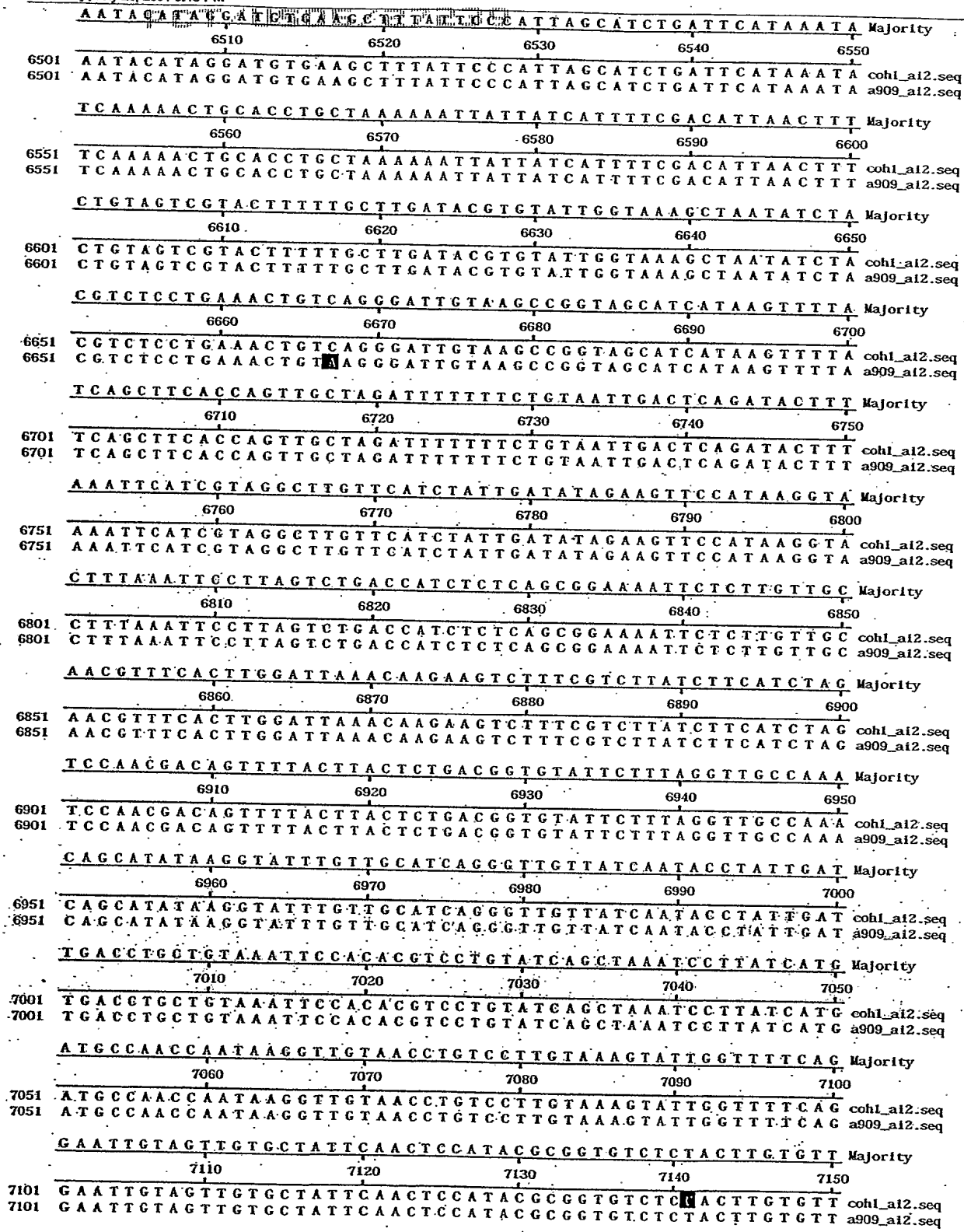
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FIGURE 21J

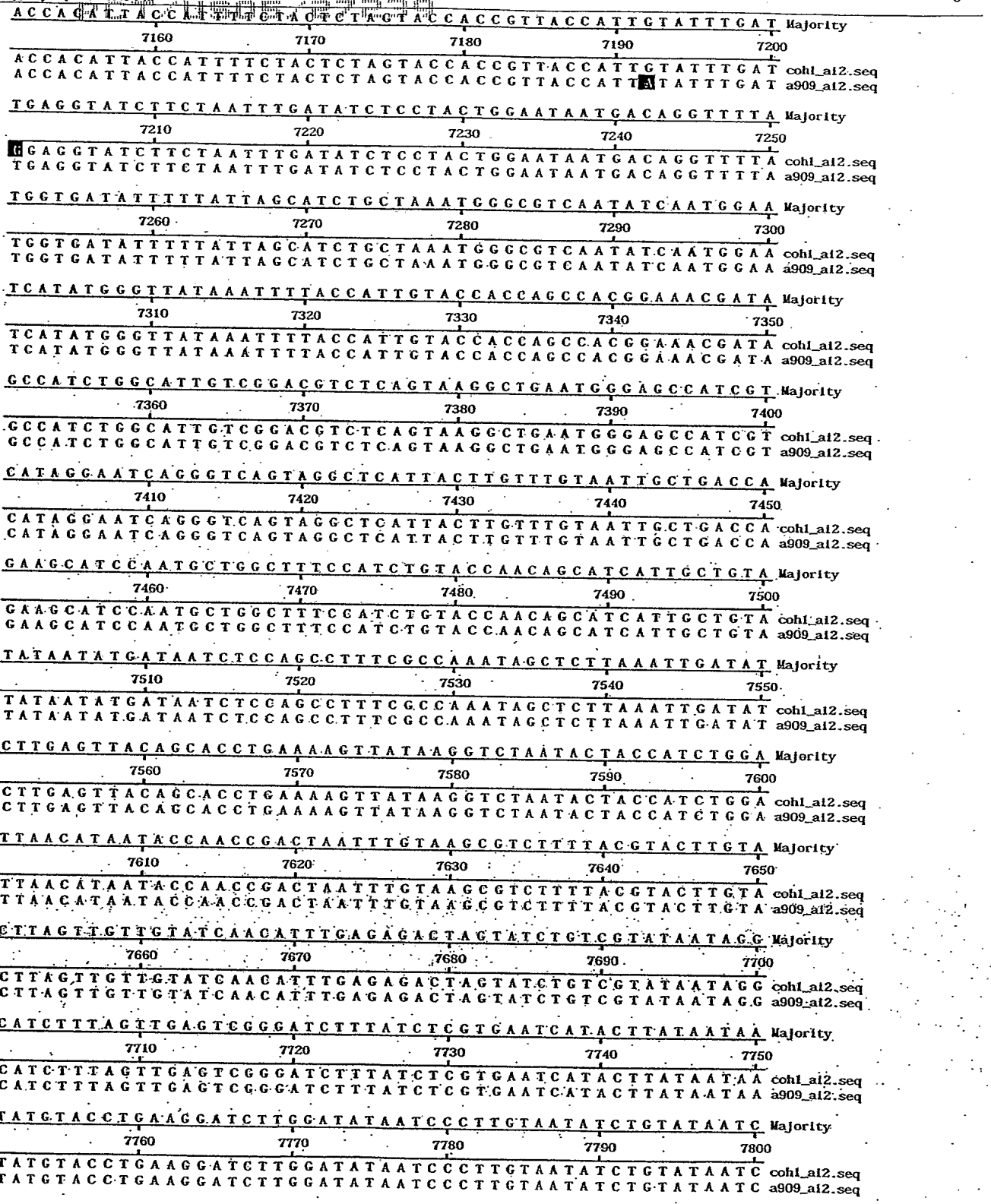
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FIGURE 21K

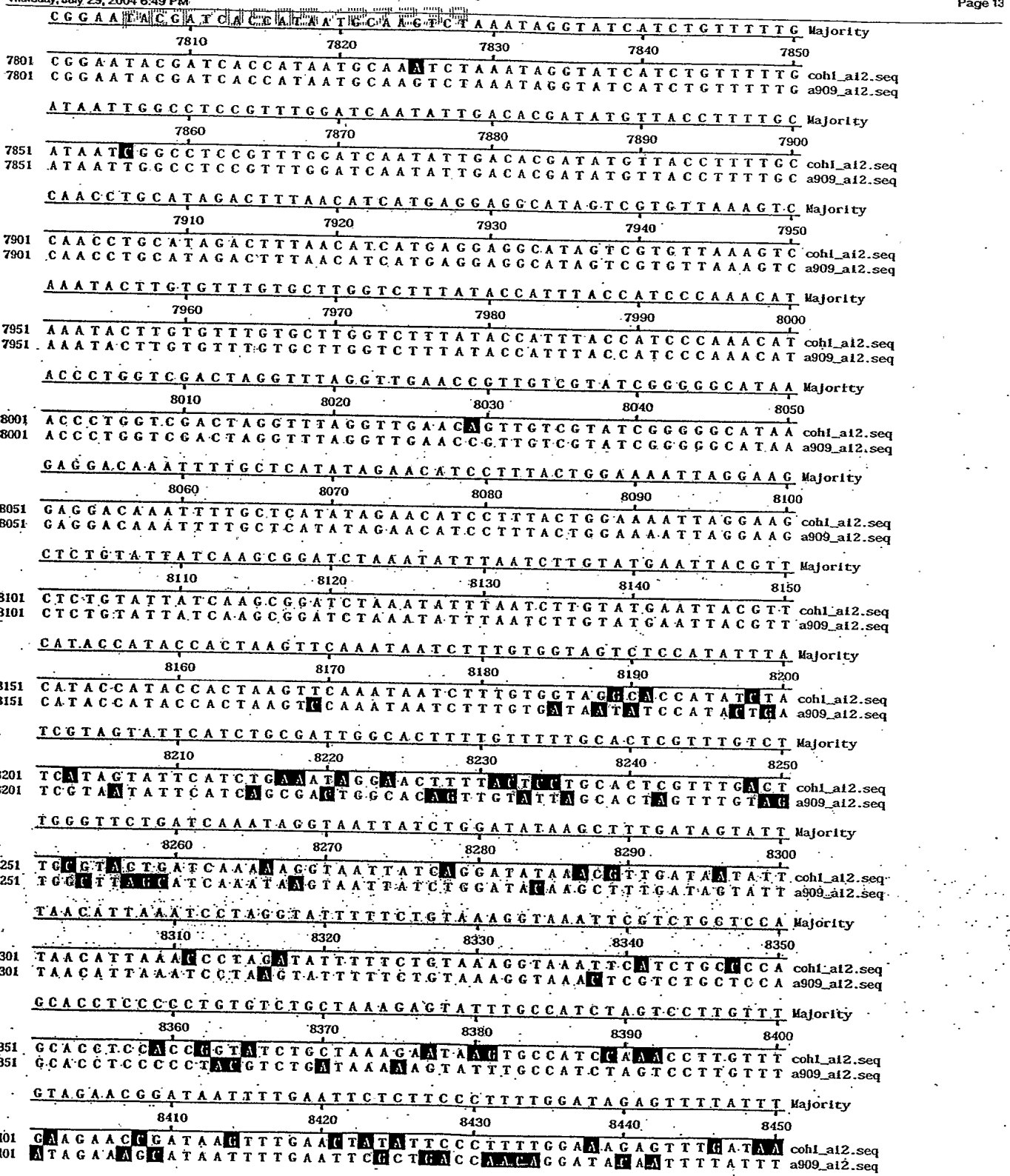
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FIGURE 21L

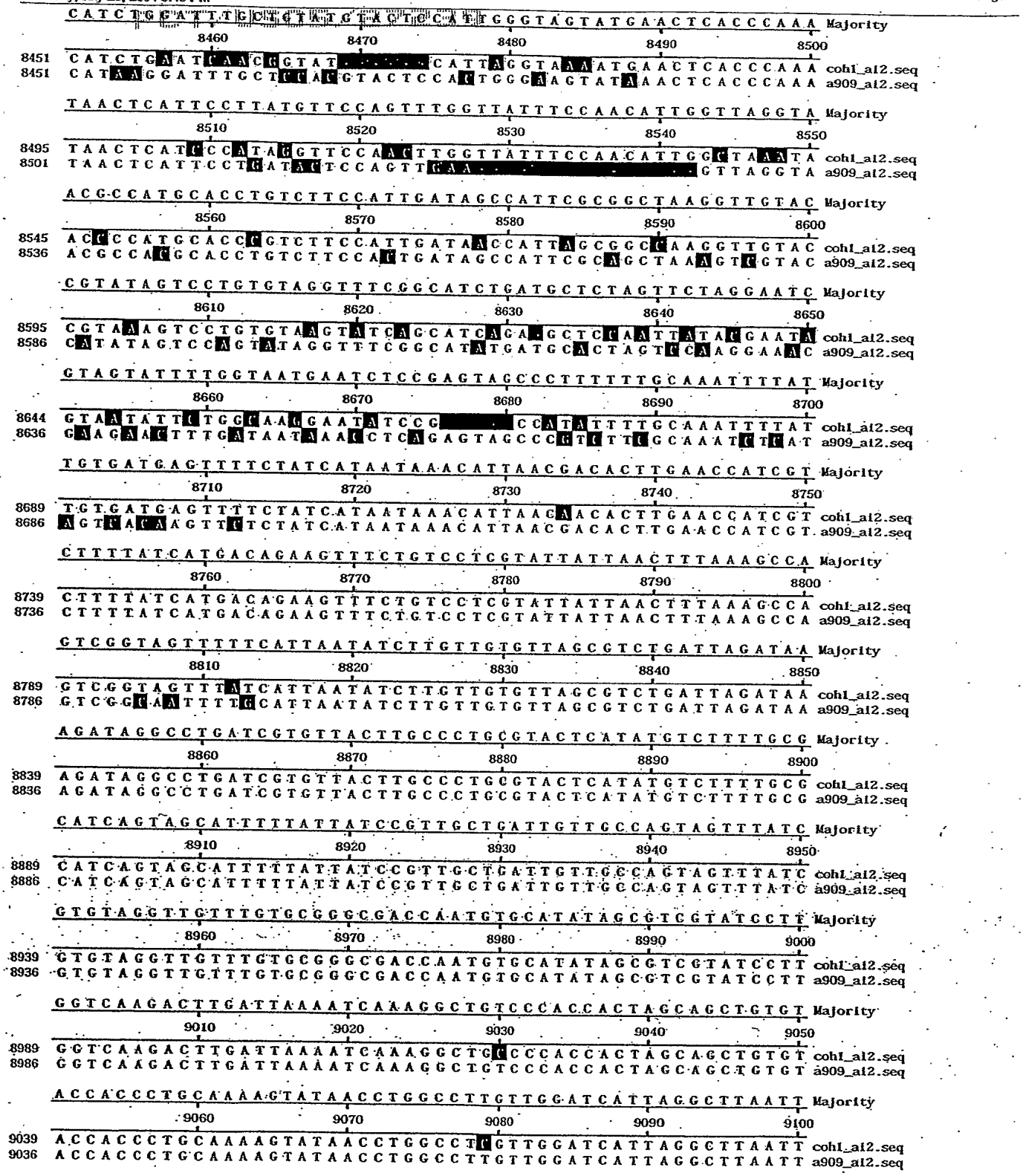
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FIGURE 21M

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FIGURE 21N

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                TACTGGGGCTTGGGGTTCTGCTTCTTTACCATTTGACTCAATAGTAATGT Majority
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FIGURE 21O

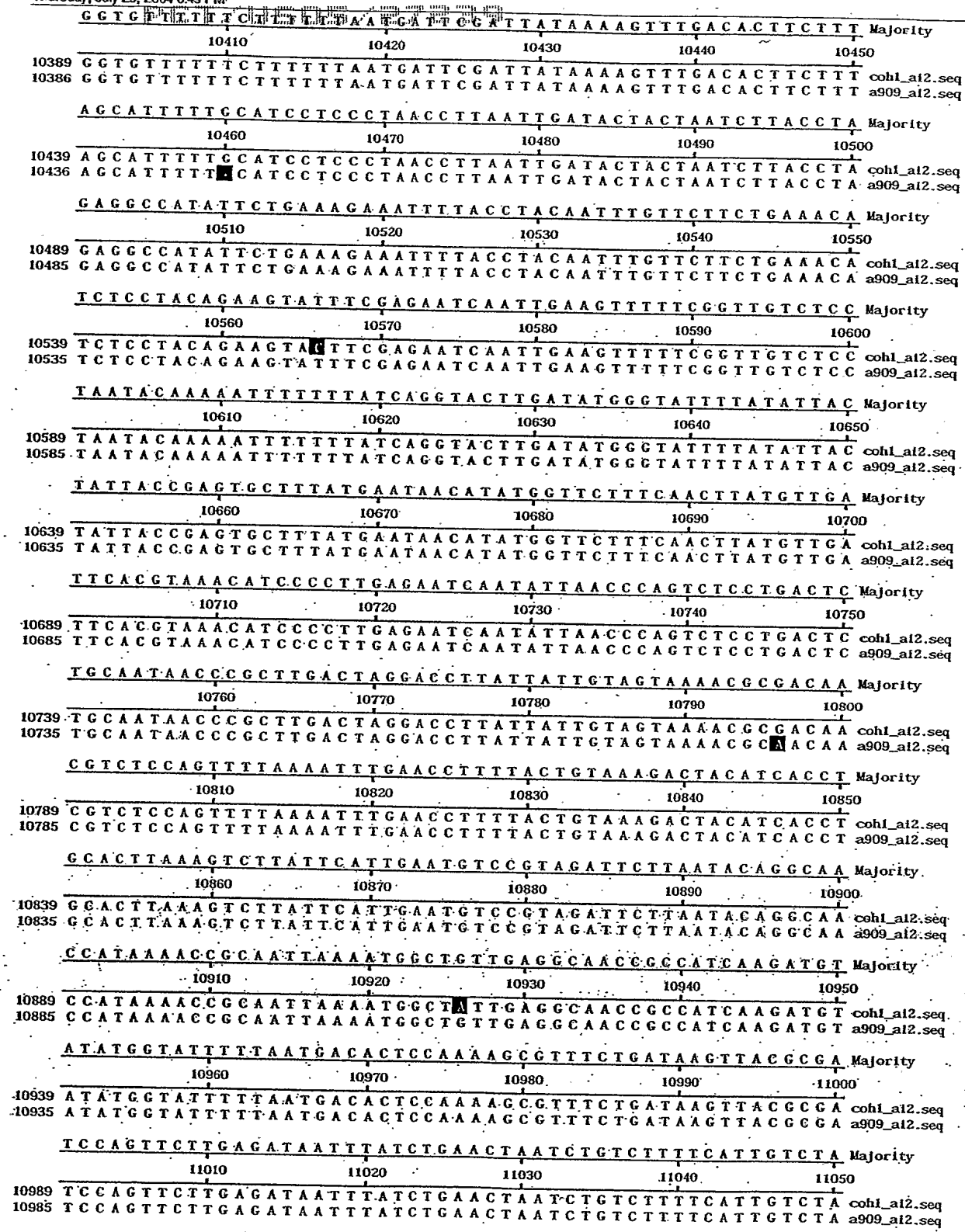
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FIGURE 21P

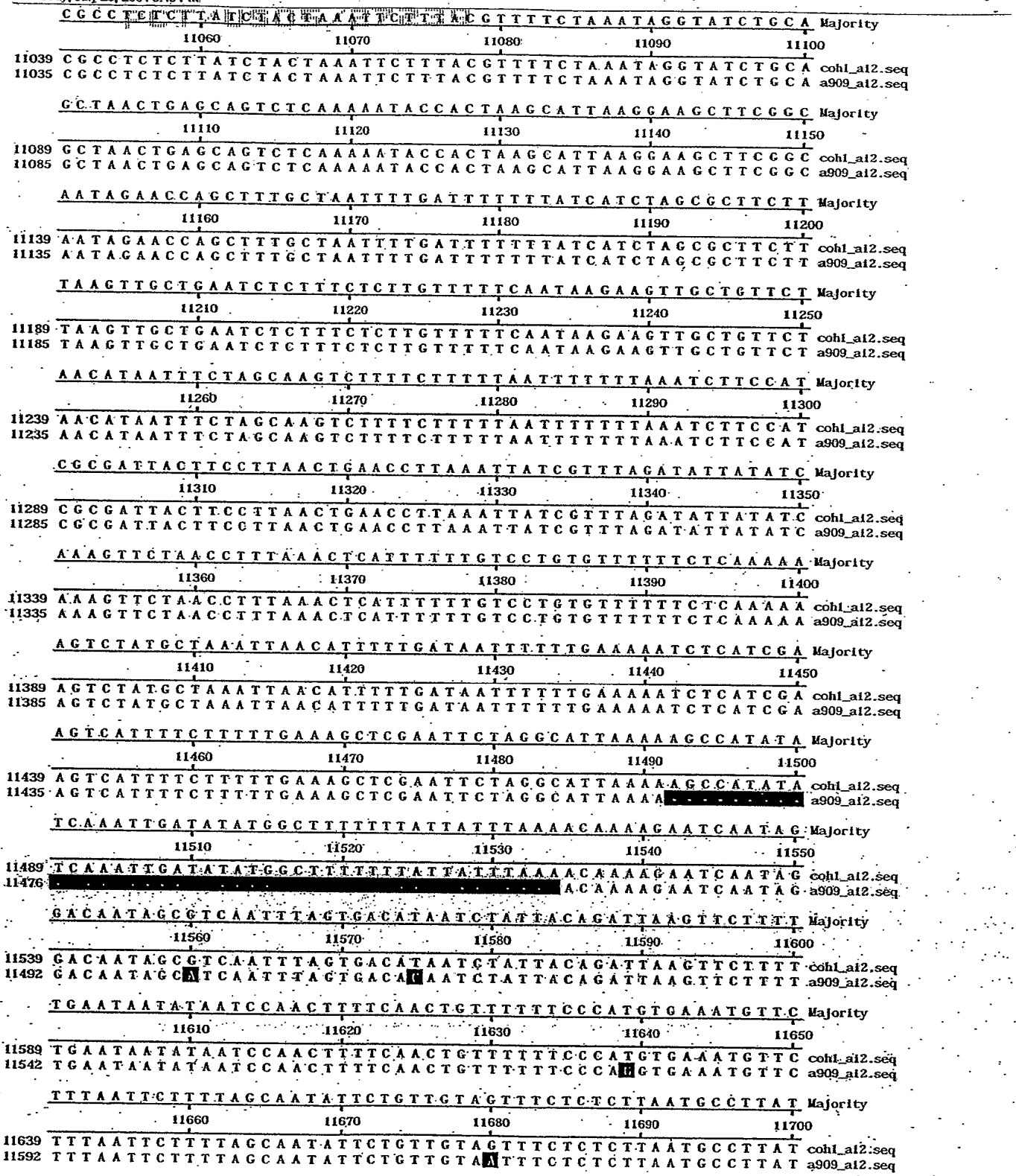
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FIGURE 21Q

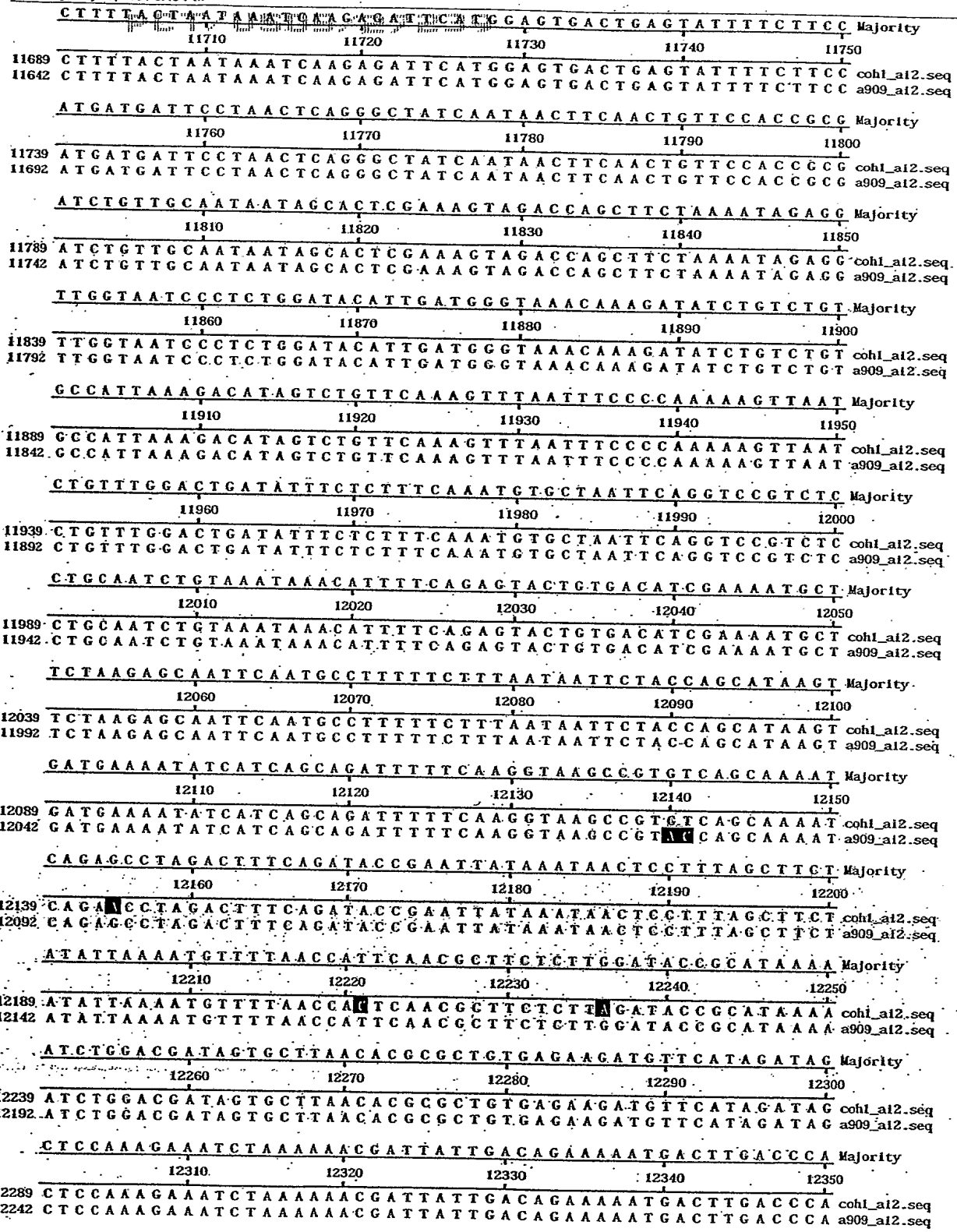
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FIGURE 21R

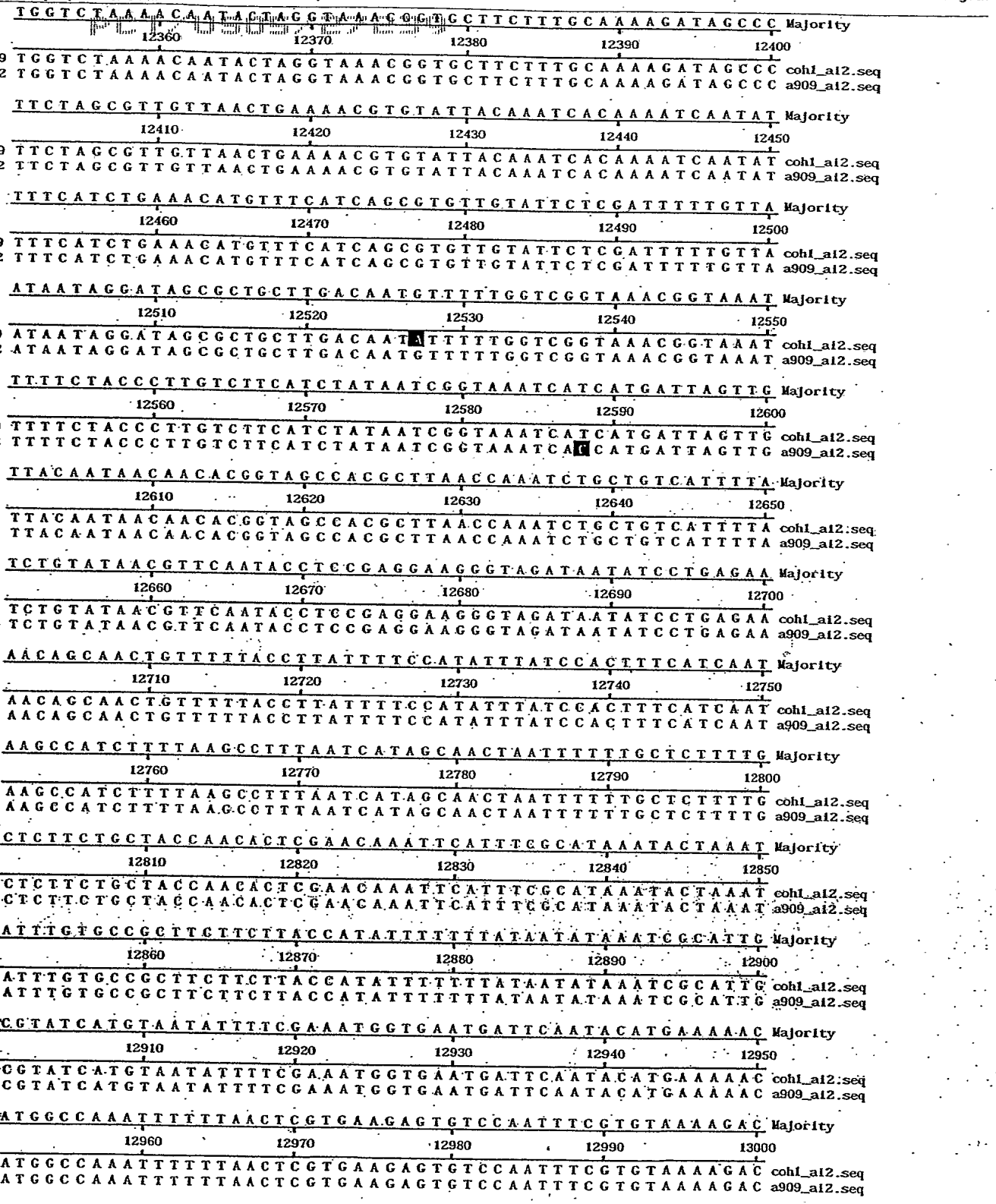
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FIGURE 21S

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                    13310       13320       13330       13340       13350
13289 AAGTCAAGAACCAATCAAATTCTTGTGCTACTGCAAATTGACCGATACAG cohl_al2.seq
13242 AAGTCAAGAACCAATCAAATTCTTGTGCTACTGCAAATTGACCAATACAG a909_al2.seq

                TTCAAAGCATATGCAATTCCTTTATTTTCTGTTAAATAATCAACAGTTAG Majority
                    13360       13370       13380       13390       13400
13339 TTCAAAGCATATGCAATTCCTTTATTTTCTGTTAAATAATCAACAGTTAG cohl_al2.seq
13292 TTCAAAGCATATGCAATTCCTTTATTTTCTGTTAAATAATCAACAGTTAG a909_al2.seq

                GTGCCCCTCTTCATTATAATCGGCCACTAATTGAGAAATTTCTTCCTTAT Majority
                    13410       13420       13430       13440       13450
13389 GTGCCCCTCTTCATTATAATCGGCCACTAATTGAGAAATTTCTTCCTTAT cohl_al2.seq
13342 GTGCCCCTCTTCATTATAATCGGCCACTAATTGAGAAATTTCGTCCTTAT a909_al2.seq

                TTTTCGAGCCATTATCTACGATGTAGATATGGCTTACTTGAGGATAAATT Majority
                    13460       13470       13480       13490       13500
13439 TTTTCGAGCCATTATCTACGATGTAGATATGGCTTACTTGAGGATAAATT cohl_al2.seq
13392 TTTTCGAGCCATTATCTACGATGTAGATATGGCTTACTTGAGGATAAATT a909_al2.seq

                GCTCGAATGTTCTGATCTAAGCGTTCAATATTGGGGTTAAAGGTGACAAT Majority
                    13510       13520       13530       13540       13550
13489 GCTCGAATGTTCTGATCTAAGCGTTCAATATTGGGGTTAAAGGTGACAAT cohl_al2.seq
13442 GCTCGAATGTTCTGATCTAAGCGTTCAATATTGGGGTTAAAGGTGACAAT a909_al2.seq

                ACCCGCTAAATATTTCATGTTCTATGCTCTTTTCTAAAATCTCTAAATAA Majority
                    13560       13570       13580       13590       13600
13539 ACCCGCTAAATATTTCATGTTCTATGCTCTTTTCTAAAATCTCTAAATAA cohl_al2.seq
13492 ACCCGCTAAATATTTCATGTTCTATGCTCTTTTCTAAAATCTCTAAATAA a909_al2.seq

                CTGAATGACTGGTGCTTTGGTTATAAAAACGATACCGACATAGATAGTTA Majority
                    13610       13620       13630       13640       13650
13589 CTGAATGACTGGTGCTTTGGTTATAAAAACGATACCGACATAGATAGTTA cohl_al2.seq
13542 CTGAATGACTGGTGCTTTGGTTATAAAAACGATACCGACATAGATAGTTA a909_al2.seq
```

FIGURE 21T

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                CTGCTACTAAACTTTGAATGACATAATTTACCAATGATACTGACATTTGA Majority
                    13660       13670       13680       13690       13700
13639 CTGCTACTAAACTTTGAATGACATAATTTACCAATGATACTGACATTTGA cohl_al2.seq
13592 CTGCTACTAAACTTTGAATGACATAATTTACCAATGATACTGACATTTGA a909_al2.seq

                GTATTGATATAATAGAGTACAGCTCCACTAAGAGTAGCAGCAATTAAATA Majority
                    13710       13720       13730       13740       13750
13689 GTATTGATATAATAAAGCTACAGCTCCACTAAGAGTAGCAGCAATTAAATA cohl_al2.seq
13642 GTATTGATATAATAGAGTACAGCTCCACTAAGAGTAGCAGCAATTAAATA a909_al2.seq

                GCGCAGCATTCCTCTTGTTAATTCTTTAAAAGTAAATACATCTCTTAAAG Majority
                    13760       13770       13780       13790       13800
13739 GCGCAGCATTCCTCTTGTTAATTCTTTAAAAGTAAATACATCTCTTAAAG cohl_al2.seq
13692 GCGCAGCATTCCTCTTGTTAATTCTTTAAAAGTAAATACATCTCTTAAAG a909_al2.seq

                AGATAGCTTGATATAGGGAGACAATAAATTCAGTAATAACTGTAGAGATA Majority
                    13810       13820       13830       13840       13850
13789 AGATAGCTTGATAGAGGGAGACAATAAATTCAGTAATAACTGTAGAGATA cohl_al2.seq
13742 AGATAGCTTGATATAGAGAGACAATAAATTCAGTAATAACTGTAGAGATA a909_al2.seq

                ATAGCTCCCATAGCACCTAAAATTGGTATTAAAAGTATATTAAGCACAAC Majority
                    13860       13870       13880       13890       13900
13839 ATAGCTCCCATAGCACCTAAAATTGGTATTAAAAGTATATTAAGCACAAC cohl_al2.seq
13792 ATAGCTCCCATAGCACCTAAAATTGGTATTAAAAGTATATTAAGCACAAC a909_al2.seq

                ATTTGCCACAAGTCCAATAACTGCAGACATTGTGTAAGCTTTTGTACGTC Majority
                    13910       13920       13930       13940       13950
13889 ATTTGCCACAAGTCCAATAACTGCAGACATTGTGTAAGCTTTTGTACGTC cohl_al2.seq
13842 ATTTGCCACAAGTCCAATAACTGCAGACATTGTGTAAGCTTTTGTACGTC a909_al2.seq

                TTGAAGCCAGTAGATACTGTGTCCCTAAAGCGTTACCATAAGAAATGCAA Majority
                    13960       13970       13980       13990       14000
13939 TTGAAGCCAGTAGATACTGTGTCCCTAAAGCGTTACCATAAGAAATGCAA cohl_al2.seq
13892 TTGAAGCCAGTAGATACTGTGTCCCTAAAGCGTTACCATAAGAAATGCAA a909_al2.seq

                ATGATCATCAAA                                        Majority
                    14010
13989 ATGATCATCAAA                                                  cohl_al2.seq
13942 ATGATCATCAAA                                                  a909_al2.seq
```

Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

FIGURE 21U

Alignment Report of gbs..., using Clustal method with PAM250 residue weight table.
Thursday, July 29, 2004 6:57 PM


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    M K L S K K L L F S A A V L T M V A G S T V E P V A Q F A T G M S I V R A A E V S Q E R P A K T T V  Majority
                      10                  20                  30                  40                  50
  1 M K L S K K L L F S A A V L T M V A G S T V E P V A Q F A T G M S I V R A A E V S Q E R P A K T T V  sag645_2603.pep
  1 M K L S K K L L F S A A V L T I V A G S T V E P V A Q F A T G M S I V R A A E V S Q E R P A K T T V  sag645_a909.pep
  1 M K L S K K L L F S A A V L T I V A G S T V E P V A Q F A T G M S I V R A A E V S Q E R P A K T T V  sag645_cjb111.pep
  1 M K L S K K L L F S A A V L T M V A G S T V E P V A Q F A T G M S I V R A A E V S Q E R P A K T T V  sag645_coh1.pep
  1 M K L S K K L L F S A A V L T M V A G S T V E P V A Q F A T G M S I V R A A E V S Q E R P A K T T V  sag645_nem316.pep

    N I Y K L Q A D S Y K S E I T S N G G I E N K D G E V I S N Y A K L G D N V K G L Q G V Q F K R Y K  Majority
                      60                  70                  80                  90                 100
 51 N I Y K L Q A D S Y K S E I T S N G G I E N K D G E V I S N Y A K L G D N V K G L Q G V Q F K R Y K  sag645_2603.pep
 51 N I Y K L Q A D S Y K S E I T S N G G I E N K D G E V I S N Y A K L G D N V K G L Q G V Q F K R Y K  sag645_a909.pep
 51 N I Y K L Q A D S Y K S E I T S N G G I E N K D G E V I S N Y A K L G D N V K G L Q G V Q F K R Y K  sag645_cjb111.pep
 51 N I Y K L Q A D S Y K S E I T S N G G I E N K D G E V I S N Y A K L G D N V K G L Q G V Q F K R Y K  sag645_coh1.pep
 51 N I Y K L Q A D S Y K S E I T S N G G I E N K D G E V I S N Y A K L G D N V K G L Q G V Q F K R Y K  sag645_nem316.pep

    V K T D I S V D E L K K L T T V E A A D A K V G T I L E E G V S L P Q K T N A Q G L V V D A L D S K  Majority
                     110                 120                 130                 140                 150
101 V K T D I S V D E L K K L T T V E A A D A K V G T I L E E G V S L P Q K T N A Q G L V V D A L D S K  sag645_2603.pep
101 V K T D I S V D E L K K L T T V E A A D A K V G T I L E E G V S L P Q K T N A Q G L V V D A L D S K  sag645_a909.pep
101 V K T D I S V D E L K K L T T V E A A D A K V G T I L E E G V S L P Q K T N A Q G L V V D A L D S K  sag645_cjb111.pep
101 V K T D I S V D E L K K L T T V E A A D A K V G T I L E E G V S L P Q K T N A Q G L V V D A L D S K  sag645_coh1.pep
101 V K T D I S V D E L K K L T T V E A A D A K V G T I L E E G V S L P Q K T N A Q G L V V D A L D S K  sag645_nem316.pep

    S N V R Y L Y V E D L K N S P S N I T K A Y A V P F V L E L P V A N S T G T G F L S E I N I Y P K N  Majority
                     160                 170                 180                 190                 200
151 S N V R Y L Y V E D L K N S P S N I T K A Y A V P F V L E L P V A N S T G T G F L S E I N I Y P K N  sag645_2603.pep
151 S N V R Y L Y V E D L K N S P S N I T K A Y A V P F V L E L P V A N S T G T G F L S E I N I Y P K N  sag645_a909.pep
151 S N V R Y L Y V E D L K N S P S N I T K A Y A V P F V L E L P V A N S T G T G F L S E I N I Y P K N  sag645_cjb111.pep
151 S N V R Y L Y V E D L K N S P S N I T K A Y A V P F V L E L P V A N S T G T G F L S E I N I Y P K N  sag645_coh1.pep
151 S N V R Y L Y V E D L K N S P S N I T K A Y A V P F V L E L P V A N S T G T G F L S E I N I Y P K N  sag645_nem316.pep

    V V T D E P K T D K D V K K L G Q D D A G Y T I G E E F K W F L K S T I P A N L G D Y E K F E I T D  Majority
                     210                 220                 230                 240                 250
201 V V T D E P K T D K D V K K L G Q D D A G Y T I G E E F K W F L K S T I P A N L G D Y E K F E I T D  sag645_2603.pep
201 V V T D E P K T D K D V K K L G Q D D A G Y T I G E E F K W F L K S T I P A N L G D Y E K F E I T D  sag645_a909.pep
201 V V T D E P K T D K D V K K L G Q D D A G Y T I G E E F K W F L K S T I P A N L G D Y E K F E I T D  sag645_cjb111.pep
201 V V T D E P K T D K D V K K L G Q D D A G Y T I G E E F K W F L K S T I P A N L G D Y E K F E I T D  sag645_coh1.pep
201 V V T D E P K T D K D V K K L G Q D D A G Y T I G E E F K W F L K S T I P A N L G D Y E K F E I T D  sag645_nem316.pep

    K F A D G L T Y K S V G K I K I G S K T L N R D E H Y T I D E P T V D N Q N T L K I T F K P E K F K  Majority
                     260                 270                 280                 290                 300
251 K F A D G L T Y K S V G K I K I G S K T L N R D E H Y T I D E P T V D N Q N T L K I T F K P E K F K  sag645_2603.pep
251 K F A D G L T Y K S V G K I K I G S K T L N R D E H Y T I D E P T V D N Q N T L K I T F K P E K F K  sag645_a909.pep
251 K F A D G L T Y K S V G K I K I G S K T L N R D E H Y T I D E P T V D N Q N T L K I T F K P E K F K  sag645_cjb111.pep
251 K F A D G L T Y K S V G K I K I G S K T L N R D E H Y T I D E P T V D N Q N T L K I T F K P E K F K  sag645_coh1.pep
251 K F A D G L T Y K S V G K I K I G S K T L N R D E H Y T I D E P T V D N Q N T L K I T F K P E K F K  sag645_nem316.pep

    E I A E L L K G M T L V K N Q D A L D K A T A N T D D A A F L E I P V A S T I N E K A V L G K A I E  Majority
                     310                 320                 330                 340                 350
301 E I A E L L K G M T L V K N Q D A L D K A T A N T D D A A F L E I P V A S T I N E K A V L G K A I E  sag645_2603.pep
301 E I A E L L K G M T L V K N Q D A L D K A T A N T D D A A F L E I P V A S T I N E K A V L G K A I E  sag645_a909.pep
301 E I A E L L K G M T L V K N Q D A L D K A T A N T D D A A F L E I P V A S T I N E K A V L G K A I E  sag645_cjb111.pep
301 E I A E L L K G M T L V K N Q D A L D K A T A N T D D A A F L E I P V A S T I N E K A V L G K A I E  sag645_coh1.pep
301 E I A E L L K G M T L V K N Q D A L D K A T A N T D D A A F L E I P V A S T I N E K A V L G K A I E  sag645_nem316.pep

    N T F E L Q Y D H T P D K A D N P K P S N P P R K P E V H T G G K R F V K K D S T E T Q T L G G A E  Majority
                     360                 370                 380                 390                 400
351 N T F E L Q Y D H T P D K A D N P K P S N P P R K P E V H T G G K R F V K K D S T E T Q T L G G A E  sag645_2603.pep
351 N T F E L Q Y D H T P D K A D N P K P S N P P R K P E V H T G G K R F V K K D S T E T Q T L G G A E  sag645_a909.pep
351 N T F E L Q Y D H T P D K A D N P K P S N P P R K P E V H T G G K R F V K K D S T E T Q T L G G A E  sag645_cjb111.pep
351 N T F E L Q Y D H T P D K A D N P K P S N P P R K P E V H T G G K R F V K K D S T E T Q T L G G A E  sag645_coh1.pep
351 N T F E L Q Y D H T P D K A D N P K P S N P P R K P E V H T G G K R F V K K D S T E T Q T L G G A E  sag645_nem316.pep
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Figure 22

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   F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K  Majority
                410       420       430       440       450
401 F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K  sag645_2603.pep
401 F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K  sag645_a909.pep
401 F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K  sag645_cjb111.pep
401 F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K  sag645_coh1.pep
401 F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K  sag645_nem316.pep

   G L A Y A V D A N A E G T A V T Y K L K E T K A P E G Y V I P D K E I E F T V S Q T S Y N T K P T D  Majority
                460       470       480       490       500
451 G L A Y A V D A N A E G T A V T Y K L K E T K A P E G Y V I P D K E I E F T V S Q T S Y N T K P T D  sag645_2603.pep
451 G L A Y A V D A N A E G T A V T Y K L K E T K A P E G Y V I P D K E I E F T V S Q T S Y N T K P T D  sag645_a909.pep
451 G L A Y A V D A N A E G T A V T Y K L K E T K A P E G Y V I P D K E I E F T V S Q T S Y N T K P T D  sag645_cjb111.pep
451 G L A Y A V D A N A E G T A V T Y K L K E T K A P E G Y V I P D K E I E F T V S Q T S Y N T K P T D  sag645_coh1.pep
451 G L A Y A V D A N A E G T A V T Y K L K E T K A P E G Y V I P D K E I E F T V S Q T S Y N T K P T D  sag645_nem316.pep

   I T V D S A D A T P D T I K N N K R P S I P N T G G I G T A I F V A I G A A V M A F A V K G M K R R  Majority
                510       520       530       540       550
501 I T V D S A D A T P D T I K N N K R P S I P N T G G I G T A I F V A I G A A V M A F A V K G M K R R  sag645_2603.pep
501 I T V D S A D A T P D T I K N N K R P S I P N T G G I G T A I F V A I G A A V M A F A V K G M K R R  sag645_a909.pep
501 I T V D S A D A T P D T I K N N K R P S I P N T G G I G T A I F V A I G A A V M A F A V K G M K R R  sag645_cjb111.pep
501 I T V D S A D A T P D T I K N N K R P S I P N T G G I G T A I F V A I G A A V M A F A V K G M K R R  sag645_coh1.pep
501 I T V D S A D A T P D T I K N N K R P S I P N T G G I G T A I F V A I G A A V M A F A V K G M K R R  sag645_nem316.pep

   T K D N                                                                                          Majority

551 T K D N                                                                                          sag645_2603.pep
551 T K D N                                                                                          sag645_a909.pep
551 T K D N                                                                                          sag645_cjb111.pep
551 T K D N                                                                                          sag645_coh1.pep
551 T K D N                                                                                          sag645_nem316.pep
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ecoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

FIGURE 22A

```
MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNA Majority
         10        20        30        40        50
1  MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNA sag649_2603.pep
1  MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNA sag649_coh1.pep
1  MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNA sag649_cjb111.pep
1  MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNA sag649_18rs21.pep
1  MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNA sag649_nem316.pep
1  MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNA sag649_cjb111.pep

TPLGKATFVLKNDNDKSETSHETVEGSGEATFENIKPGDYTLREETAPIG Majority
         60        70        80        90       100
51 TPLGKATFVLKNDNDKSETSHETVEGSGEATFENIKPGDYTLREETAPIG sag649_2603.pep
51 TPLGKATFVLKNDNDKSETSHETVEGSGEATFENIKPGDYTLREETAPIG sag649_coh1.pep
51 TPLGKATFVLKNDNDKSETSHETVEGSGEATFENIKPGDYTLREETAPIG sag649_cjb111.pep
51 TPLGKATFVLKNDNDKSETSHETVEGSGEATFENIKPGDYTLREETAPIG sag649_18rs21.pep
51 TPLGKATFVLKNDNDKSETSHETVEGSGEATFENIKPGDYTLREETAPIG sag649_nem316.pep
51 TPLGKATFVLKNDNDKSETSHETVEGSGEATFENIKPGDYTLREETAPIG sag649_cjb111.pep

YKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKE Majority
        110       120       130       140       150
101 YKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKE sag649_2603.pep
101 YKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKE sag649_coh1.pep
101 YKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKE sag649_cjb111.pep
101 YKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKE sag649_18rs21.pep
101 YKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKE sag649_nem316.pep
101 YKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKE sag649_cjb111.pep

NYPLVNVEGSKVGEQYKALNPINGKDGRREIAEGWLSKKITGVNDLDKNK Majority
        160       170       180       190       200
151 NYPLVNVEGSKVGEQYKALNPINGKDGRREIAEGWLSKKITGVNDLDKNK sag649_2603.pep
151 NYPLVNVEGSKVGEQYKALNPINGKDGRREIAEGWLSKKITGVNDLDKNK sag649_coh1.pep
151 NYPLVNVEGSKVGEQYKALNPINGKDGRREIAEGWLSKKITGVNDLDKNK sag649_cjb111.pep
151 NYPLVNVEGSKVGEQYKALNPINGKDGRREIAEGWLSKKITGVNDLDKNK sag649_18rs21.pep
151 NYPLVNVEGSKVGEQYKALNPINGKDGRREIAEGWLSKKITGVNDLDKNK sag649_nem316.pep
151 NYPLVNVEGSKVGEQYKALNPINGKDGRREIAEGWLSKKITGVNDLDKNK sag649_cjb111.pep

YKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGE Majority
        210       220       230       240       250
201 YKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGE sag649_2603.pep
201 YKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGE sag649_coh1.pep
201 YKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGE sag649_cjb111.pep
201 YKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGE sag649_18rs21.pep
201 YKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGE sag649_nem316.pep
201 YKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGE sag649_cjb111.pep

AVEKLIDKITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSV Majority
        260       270       280       290       300
251 AVEKLIDKITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSV sag649_2603.pep
251 AVEKLIDKITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSV sag649_coh1.pep
251 AVEKLIDKITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSV sag649_cjb111.pep
251 AVEKLIDKITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSV sag649_18rs21.pep
251 AVEKLIDKITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSV sag649_nem316.pep
251 AVEKLIDKITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSV sag649_cjb111.pep

SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ Majority
        310       320       330       340       350
301 SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ sag649_2603.pep
301 SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ sag649_coh1.pep
301 SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ sag649_cjb111.pep
301 SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ sag649_18rs21.pep
301 SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ sag649_nem316.pep
301 SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ sag649_cjb111.pep

FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS Majority
        360       370       380       390       400
351 FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS sag649_2603.pep
351 FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS sag649_coh1.pep
351 FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS sag649_cjb111.pep
351 FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS sag649_18rs21.pep
351 FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS sag649_nem316.pep
351 FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS sag649_cjb111.pep
```

Figure 23

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    T S Y Q N Q F N S F L N K I P D R S G I L Q E D F I I N G D D Y Q I V K G D G E S F K L F S D R K V  Majority
              410                 420                 430                 440                 450
401 T S Y Q N Q F N S F L N K I P D R S G I L Q E D F I I N G D D Y Q I V K G D G E S F K L F S D R K V  sag649_2603.pep
401 T S Y Q N Q F N S F L N K I P D R S G I L Q E D F I I N G D D Y Q I V K G D G E S F K L F S D R K V  sag649_coh1.pep
401 T S Y Q N Q F N S F L N K I P D R S G I L Q E D F I I N G D D Y Q I V K G D G E S F K L F S D R K V  sag649_cjb111.pep
401 T S Y Q N Q F N S F L N K I P D R S G I L Q E D F I I N G D D Y Q I V K G D G E S F K L F S D R K V  sag649_18rs21.pep
401 T S Y Q N Q F N S F L N K I P D R S G I L Q E D F I I N G D D Y Q I V K G D G E S F K L F S D R K V  sag649_nem316.pep
401 T S Y Q N Q F N S F L N K I P D R S G I L Q E D F I I N G D D Y Q I V K G D G E S F K L F S D R K V  sag649_cjb111.pep

    P V T G G T T Q A A Y R V P Q N Q L S V M S N E G Y A I N S G Y I Y L Y W R D Y N W V Y P F D P K T  Majority
              460                 470                 480                 490                 500
451 P V T G G T T Q A A Y R V P Q N Q L S V M S N E G Y A I N S G Y I Y L Y W R D Y N W V Y P F D P K T  sag649_2603.pep
451 P V T G G T T Q A A Y R V P Q N Q L S V M S N E G Y A I N S G Y I Y L Y W R D Y N W V Y P F D P K T  sag649_coh1.pep
451 P V T G G T T Q A A Y R V P Q N Q L S V M S N E G Y A I N S G Y I Y L Y W R D Y N W V Y P F D P K T  sag649_cjb111.pep
451 P V T G G T T Q A A Y R V P Q N Q L S V M S N E G Y A I N S G Y I Y L Y W R D Y N W V Y P F D P K T  sag649_18rs21.pep
451 P V T G G T T Q A A Y R V P Q N Q L S V M S N E G Y A I N S G Y I Y L Y W R D Y N W V Y P F D P K T  sag649_nem316.pep
451 P V T G G T T Q A A Y R V P Q N Q L S V M S N E G Y A I N S G Y I Y L Y W R D Y N W V Y P F D P K T  sag649_cjb111.pep

    K K V S A T K Q I K T H G E P T T L Y F N G N I R P K G Y D I F T V G I G V N G D P G A T P L E A E  Majority
              510                 520                 530                 540                 550
501 K K V S A T K Q I K T H G E P T T L Y F N G N I R P K G Y D I F T V G I G V N G D P G A T P L E A E  sag649_2603.pep
501 K K V S A T K Q I K T H G E P T T L Y F N G N I R P K G Y D I F T V G I G V N G D P G A T P L E A E  sag649_coh1.pep
501 K K V S A T K Q I K T H G E P T T L Y F N G N I R P K G Y D I F T V G I G V N G D P G A T P L E A E  sag649_cjb111.pep
501 K K V S A T K Q I K T H G E P T T L Y F N G N I R P K G Y D I F T V G I G V N G D P G A T P L E A E  sag649_18rs21.pep
501 K K V S A T K Q I K T H G E P T T L Y F N G N I R P K G Y D I F T V G I G V N G D P G A T P L E A E  sag649_nem316.pep
501 K K V S A T K Q I K T H G E P T T L Y F N G N I R P K G Y D I F T V G I G V N G D P G A T P L E A E  sag649_cjb111.pep

    K F M Q S I S S K T E N Y T N V D D T N K I Y D E L N K Y F K T I V E E K H S I V D G N V T D P M G  Majority
              560                 570                 580                 590                 600
551 K F M Q S I S S K T E N Y T N V D D T N K I Y D E L N K Y F K T I V E E K H S I V D G N V T D P M G  sag649_2603.pep
551 K F M Q S I S S K T E N Y T N V D D T N K I Y D E L N K Y F K T I V E E K H S I V D G N V T D P M G  sag649_coh1.pep
551 K F M Q S I S S K T E N Y T N V D D T N K I Y D E L N K Y F K T I V E E K H S I V D G N V T D P M G  sag649_cjb111.pep
551 K F M Q S I S S K T E N Y T N V D D T N K I Y D E L N K Y F K T I V E E K H S I V D G N V T D P M G  sag649_18rs21.pep
551 K F M Q S I S S K T E N Y T N V D D T N K I Y D E L N K Y F K T I V E E K H S I V D G N V T D P M G  sag649_nem316.pep
551 K F M Q S I S S K T E N Y T N V D D T N K I Y D E L N K Y F K T I V E E K H S I V D G N V T D P M G  sag649_cjb111.pep

    E M I E F Q L K N G Q S F T H D D Y V L V G N D G S Q L K N G V A L G G P N S D G G I L K D V T V T  Majority
              610                 620                 630                 640                 650
601 E M I E F Q L K N G Q S F T H D D Y V L V G N D G S Q L K N G V A L G G P N S D G G I L K D V T V T  sag649_2603.pep
601 E M I E F Q L K N G Q S F T H D D Y V L V G N D G S Q L K N G V A L G G P N S D G G I L K D V T V T  sag649_coh1.pep
601 E M I E F Q L K N G Q S F T H D D Y V L V G N D G S Q L K N G V A L G G P N S D G G I L K D V T V T  sag649_cjb111.pep
601 E M I E F Q L K N G Q S F T H D D Y V L V G N D G S Q L K N G V A L G G P N S D G G I L K D V T V T  sag649_18rs21.pep
601 E M I E F Q L K N G Q S F T H D D Y V L V G N D G S Q L K N G V A L G G P N S D G G I L K D V T V T  sag649_nem316.pep
601 E M I E F Q L K N G Q S F T H D D Y V L V G N D G S Q L K N G V A L G G P N S D G G I L K D V T V T  sag649_cjb111.pep

    Y D K T S Q T I K I N H L N L G S G Q K V V L T Y D V R L K D N Y I S N K F Y N T N N R T T L S P K  Majority
              660                 670                 680                 690                 700
651 Y D K T S Q T I K I N H L N L G S G Q K V V L T Y D V R L K D N Y I S N K F Y N T N N R T T L S P K  sag649_2603.pep
651 Y D K T S Q T I K I N H L N L G S G Q K V V L T Y D V R L K D N Y I S N K F Y N T N N R T T L S P K  sag649_coh1.pep
651 Y D K T S Q T I K I N H L N L G S G Q K V V L T Y D V R L K D N Y I S N K F Y N T N N R T T L S P K  sag649_cjb111.pep
651 Y D K T S Q T I K I N H L N L G S G Q K V V L T Y D V R L K D N Y I S N K F Y N T N N R T T L S P K  sag649_18rs21.pep
651 Y D K T S Q T I K I N H L N L G S G Q K V V L T Y D V R L K D N Y I S N K F Y N T N N R T T L S P K  sag649_nem316.pep
651 Y D K T S Q T I K I N H L N L G S G Q K V V L T Y D V R L K D N Y I S N K F Y N T N N R T T L S P K  sag649_cjb111.pep

    S E K E P N T I R D F P I P K I R D V R E F P V L T I S N Q K K M G E V E F I K V N K D K H S E S L  Majority
              710                 720                 730                 740                 750
701 S E K E P N T I R D F P I P K I R D V R E F P V L T I S N Q K K M G E V E F I K V N K D K H S E S L  sag649_2603.pep
701 S E K E P N T I R D F P I P K I R D V R E F P V L T I S N Q K K M G E V E F I K V N K D K H S E S L  sag649_coh1.pep
701 S E K E P N T I R D F P I P K I R D V R E F P V L T I S N Q K K M G E V E F I K V N K D K H S E S L  sag649_cjb111.pep
701 S E K E P N T I R D F P I P K I R D V R E F P V L T I S N Q K K M G E V E F I K V N K D K H S E S L  sag649_18rs21.pep
701 S E K E P N T I R D F P I P K I R D V R E F P V L T I S N Q K K M G E V E F I K V N K D K H S E S L  sag649_nem316.pep
701 S E K E P N T I R D F P I P K I R D V R E F P V L T I S N Q K K M G E V E F I K V N K D K H S E S L  sag649_cjb111.pep

    L G A K F Q L Q I E K D F S G Y K Q F V P E G S D V T T K N D G K I Y F K A L Q D G N Y K L Y E I S  Majority
              760                 770                 780                 790                 800
751 L G A K F Q L Q I E K D F S G Y K Q F V P E G S D V T T K N D G K I Y F K A L Q D G N Y K L Y E I S  sag649_2603.pep
751 L G A K F Q L Q I E K D F S G Y K Q F V P E G S D V T T K N D G K I Y F K A L Q D G N Y K L Y E I S  sag649_coh1.pep
751 L G A K F Q L Q I E K D F S G Y K Q F V P E G S D V T T K N D G K I Y F K A L Q D G N Y K L Y E I S  sag649_cjb111.pep
751 L G A K F Q L Q I E K D F S G Y K Q F V P E G S D V T T K N D G K I Y F K A L Q D G N Y K L Y E I S  sag649_18rs21.pep
751 L G A K F Q L Q I E K D F S G Y K Q F V P E G S D V T T K N D G K I Y F K A L Q D G N Y K L Y E I S  sag649_nem316.pep
751 L G A K F Q L Q I E K D F S G Y K Q F V P E G S D V T T K N D G K I Y F K A L Q D G N Y K L Y E I S  sag649_cjb111.pep
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FIGURE 23A

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     S P D G Y I E V K T K P V V T F T I Q N G E V T N L K A D P N A N K N Q I G Y L E G N G K H L I T N  Majority
                              810                 820                 830                 840                 850
801  S P D G Y I E V K T K P V V T F T I Q N G E V T N L K A D P N A N K N Q I G Y L E G N G K H L I T N  sag649_2603.pep
801  S P D G Y I E V K T K P V V T F T I Q N G E V T N L K A D P N A N K N Q I G Y L E G N G K H L I T N  sag649_coh1.pep
801  S P D G Y I E V K T K P V V T F T I Q N G E V T N L K A D P N A N K N Q I G Y L E G N G K H L I T N  sag649_cjb111.pep
801  S P D G Y I E V K T K P V V T F T I Q N G E V T N L K A D P N A N K N Q I G Y L E G N G K H L I T N  sag649_18rs21.pep
801  S P D G Y I E V K T K P V V T F T I Q N G E V T N L K A D P N A N K N Q I G Y L E G N G K H L I T N  sag649_nem316.pep
801  S P D G Y I E V K T K P V V T F T I Q N G E V T N L K A D P N A N K N Q I G Y L E G N G K H L I T N  sag649_cjb111.pep

     T P K R P P G V F P K T G G I G T I V Y I L V G S T F M I L T I C S F R R K Q L  Majority
                              860                 870                 880                 890
851  T P K R P P G V F P K T G G I G T I V Y I L V G S T F M I L T I C S F R R K Q L  sag649_2603.pep
851  T P K R P P G V F P K T G G I G T I V Y I L V G S T F M I L T I C S F R R K Q L  sag649_coh1.pep
851  T P K R P P G V F P K T G G I G T I V Y I L V G S T F M I L T I C S F R R K Q L  sag649_cjb111.pep
851  T P K R P P G V F P K T G G I G T I V Y I L V G S T F M I L T I C S F R R K Q L  sag649_18rs21.pep
851  T P K R P P G V F P K T G G I G T I V Y I L V G S T F M I L T I C S F R R K Q L  sag649_nem316.pep
851  T P K R P P G V F P K T G G I G T I V Y I L V G S T F M I L T I C S F R R K Q L  sag649_cjb111.pep
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Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

FIGURE 23B

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    M R K Y Q K F S K I L T L S L F C L S Q I P L N T N V L G E S T V P E N G A K G K L V V K K T D D Q Majority
                      10                  20                  30                  40                  50
1   M R K Y Q K F S K I L T L S L F C L S Q I P L N T N V L G E S T V P E N G A K G K L V V K K T D D Q sag1408_2603.pep
1   M R K Y Q K F S K I L T L S L F C L S Q I P L N T N V L G E S T V P E N G A K G K L V V K K T D D Q sag1408_515.pep
1   M R K Y Q K F S K I L T L S L F C L S Q I P L N T N V L G E S T V P E N G A K G K L V V K K T D D Q sag1408_18rs21.seq
1   M R K Y Q K F S K I L T L S L F C L S Q I P L N T N V L G E S T V P E N G A K G K L V V K K T D D Q sag1408_cjb111.pep
1   M R K Y Q K F S K I L T L S L F C L S Q I P L N T N V L G E S T V P E N G A K G K L V V K K T D D Q sag1408_h36b.pep
1   M R K Y Q K F S K I L T L S L F C L S Q I P L N T N V L G E S T V P E N G A K G K L V V K K T D D Q sag1408_nem316.pep

    N K P L S K A T F V L K T T A H P E S K I E K V T A E L T G E A T F D N L I P G D Y T L S E E T A P Majority
                      60                  70                  80                  90                  100
51  N K P L S K A T F V L K T T A H P E S K I E K V T A E L T G E A T F D N L I P G D Y T L S E E T A P sag1408_2603.pep
51  N K P L S K A T F V L K T T A H P E S K I E K V T A E L T G E A T F D N L I P G D Y T L S E E T A P sag1408_515.pep
51  N K P L S K A T F V L K T T A H P E S K I E K V T A E L T G E A T F D N L I P G D Y T L S E E T A P sag1408_18rs21.seq
51  N K P L S K A T F V L K T T A H P E S K I E K V T A E L T G E A T F D N L I P G D Y T L S E E T A P sag1408_cjb111.pep
51  N K P L S K A T F V L K P T S H S E S K V E K V T I E V T G E A T F D N L I P G D Y T L S E E T A P sag1408_h36b.pep
51  N K P L S K A T F V L K T T A H P E S K I E K V T A E L T G E A T F D N L I P G D Y T L S E E T A P sag1408_nem316.pep

    E G Y K K T N Q T W Q V K V E S N G K T T I Q N S G D K N S T I G Q N Q E E L D K Q Y P P T G I Y E Majority
                      110                 120                 130                 140                 150
101 E G Y K K T N Q T W Q V K V E S N G K T T I Q N S G D K N S T I G Q N Q E E L D K Q Y P P T G I Y E sag1408_2603.pep
101 E G Y K K T N Q T W Q V K V E S N G K T T I Q N S G D K N S T I G Q N Q E E L D K Q Y P P T G I Y E sag1408_515.pep
101 E G Y K K T N Q T W Q V K V E S N G K T T I Q N S G D K N S T I G Q N Q E E L D K Q Y P P T G I Y E sag1408_18rs21.seq
101 E G Y K K T N Q T W Q V K V E S N G K T T I Q N S G D K N S T I G Q N Q E E L D K Q Y P P T G I Y E sag1408_cjb111.pep
101 E G Y K K T I Q T W Q V K V E S N G K T T I Q N S D D K K S I I K Q K Q E E L D K Q Y P I T G A Y E sag1408_h36b.pep
101 E G Y K K T N Q T W Q V K V E S N G K T T I Q N S G D K N S T I G Q N H E E L D K Q Y P P T G I Y E sag1408_nem316.pep

    D T K E S Y K L E H V K G S V P N G K S E A K A V N P Y S S E G E H I R E I P E G T L S K R I S E V Majority
                      160                 170                 180                 190                 200
151 D T K E S Y K L E H V K G S V P N G K S E A K A V N P Y S S E G E H I R E I P E G T L S K R I S E V sag1408_2603.pep
151 D T K E S Y K L E H V K G S V P N G K S E A K A V N P Y S S E G E H I R E I P E G T L S K R I S E V sag1408_515.pep
151 D T K E S Y K L E H V K G S V P N G K S E A K A V N P Y S S E G E H I R E I P E G T L S K R I S E V sag1408_18rs21.seq
151 D T K E S Y K L E H V K G S V P N G K S E A K A V N P Y S S E G E H I R E I P E G T L S K R I S E V sag1408_cjb111.pep
151 D T K E S Y A L E H V K N S I P N G K L E A K A V N P Y S S E G E H I R E I Q E G T L S K R I S E V sag1408_h36b.pep
151 D T K E S Y K L E H V K G S V P N G K S E A K A V N P Y S S E G E H I R E I P E G T L S K R I S E V sag1408_nem316.pep

    G D L A H N K Y K I E L T V S G K T I V K P V D K Q K P L D V V F V L D N S N S M N N D G P N F Q R Majority
                      210                 220                 230                 240                 250
201 G D L A H N K Y K I E L T V S G K T I V K P V D K Q K P L D V V F V L D N S N S M N N D G P N F Q R sag1408_2603.pep
201 G D L A H N K Y K I E L T V S G K T I V K P V D K Q K P L D V V F V L D N S N S M N N D G P N F Q R sag1408_515.pep
201 G D L A H N K Y K I E L T V S G K T I V K P V D K Q K P L D V V F V L D N S N S M N N D G P N F Q R sag1408_18rs21.seq
201 G D L A H N K Y K I E L T V S G K T I V K P V D K Q K P L D V V F V L D N S N S M N N D G P N F Q R sag1408_cjb111.pep
201 N D L D H N K Y K I E L T V S G K S I I K I I N K D F P L D V V F V L D N S N S M K N N G . . . . K sag1408_h36b.pep
201 G D L A H N K Y K I E L T V S G K T I V K P V D K Q K P L D V V F V L D N S N S M N N D G P N F Q R sag1408_nem316.pep

    H N K A K K A A E A L G T A V K D I L G A N S D N R V A L V T Y G S D I F D G R S V D V V K G F K E Majority
                      260                 270                 280                 290                 300
251 H N K A K K A A E A L G T A V K D I L G A N S D N R V A L V T Y G S D I F D G R S V D V V K G F K E sag1408_2603.pep
251 H N K A K K A A E A L G T A V K D I L G A N S D N R V A L V T Y G S D I F D G R S V D V V K G F K E sag1408_515.pep
251 H N K A K K A A E A L G T A V K D I L G A N S D N R V A L V T Y G S D I F D G R S V D V V K G F K E sag1408_18rs21.seq
251 H N K A K K A A E A L G T A V K D I L G A N S D N R V A L V T Y G S D I F D G R S V D V V K G F K E sag1408_cjb111.pep
247 N N K A K K A G E A V E T I I K D V L G A N V I N R A A L V T Y G S D I F D G R I V K V I K G F K E sag1408_h36b.pep
251 H N K A K K A A E A L G T A V K D I L G A N S D N R V A L V T Y G S D I F D G R S V D V V K G F K E sag1408_nem316.pep

    D D K Y Y G L Q T K F T I Q T E N Y S H K Q L T N N A E E I I K R I P T E A P K A K W G S T T N G L Majority
                      310                 320                 330                 340                 350
301 D D K Y Y G L Q T K F T I Q T E N Y S H K Q L T N N A E E I I K R I P T E A P K A K W G S T T N G L sag1408_2603.pep
301 D D K Y Y G L Q T K F T I Q T E N Y S H K Q L T N N A E E I I K R I P T E A P K A K W G S T T N G L sag1408_515.pep
301 D D K Y Y G L Q T K F T I Q T E N Y S H K Q L T N N A E E I I K R I P T E A P K A K W G S T T Y G L sag1408_18rs21.seq
301 D D K Y Y G L Q T K F T I Q T E N Y S H K Q L T N N A E E I I K R I P T E A P K A K W G S T T N G L sag1408_cjb111.pep
297 D P . Y Y G L E T S F T V Q T A D Y S Y K K E T N I A A D I I K K I P K E A P E A K W G G T S I G L sag1408_h36b.pep
301 D D K Y Y G L Q T K F T I Q T E N Y S H K Q L T N N A E E I I K R I P T E A P R A K W G S T T N G L sag1408_nem316.pep

    T P E Q Q K E Y Y L S K V G E T F T M K A F M E A D D I L S Q V N R N S Q K I I V H V T D G V P T R Majority
                      360                 370                 380                 390                 400
351 T P E Q Q K E Y Y L S K V G E T F T M K A F M E A D D I L S Q V N R N S Q K I I V H V T D G V P T R sag1408_2603.pep
351 T P E Q Q K E Y Y L S K V G E T F T M K A F M E A D D I L S Q V N R N S Q K I I V H V T D G V P T R sag1408_515.pep
351 T P E Q Q K E Y Y L S K V G E T F T M K A F M E A D D I L S Q V N R N S Q K I I V H V T D G V P T R sag1408_18rs21.seq
351 T P E Q Q K E Y Y L S K V G E T F T M K A F M E A D D I L S Q V N R N S Q K I I V H V T D G V P T R sag1408_cjb111.pep
346 T P E K K R E Y D L S K V G E T F T M K A F M E A D T T L S S T Q R K S N K I I V H I T D G V P T R sag1408_h36b.pep
351 T P E Q Q K Q Y Y L S K V G E T F T M K A F M E A D D I L S Q V D R N S Q K I I V H I T D G V P T R sag1408_nem316.pep
```
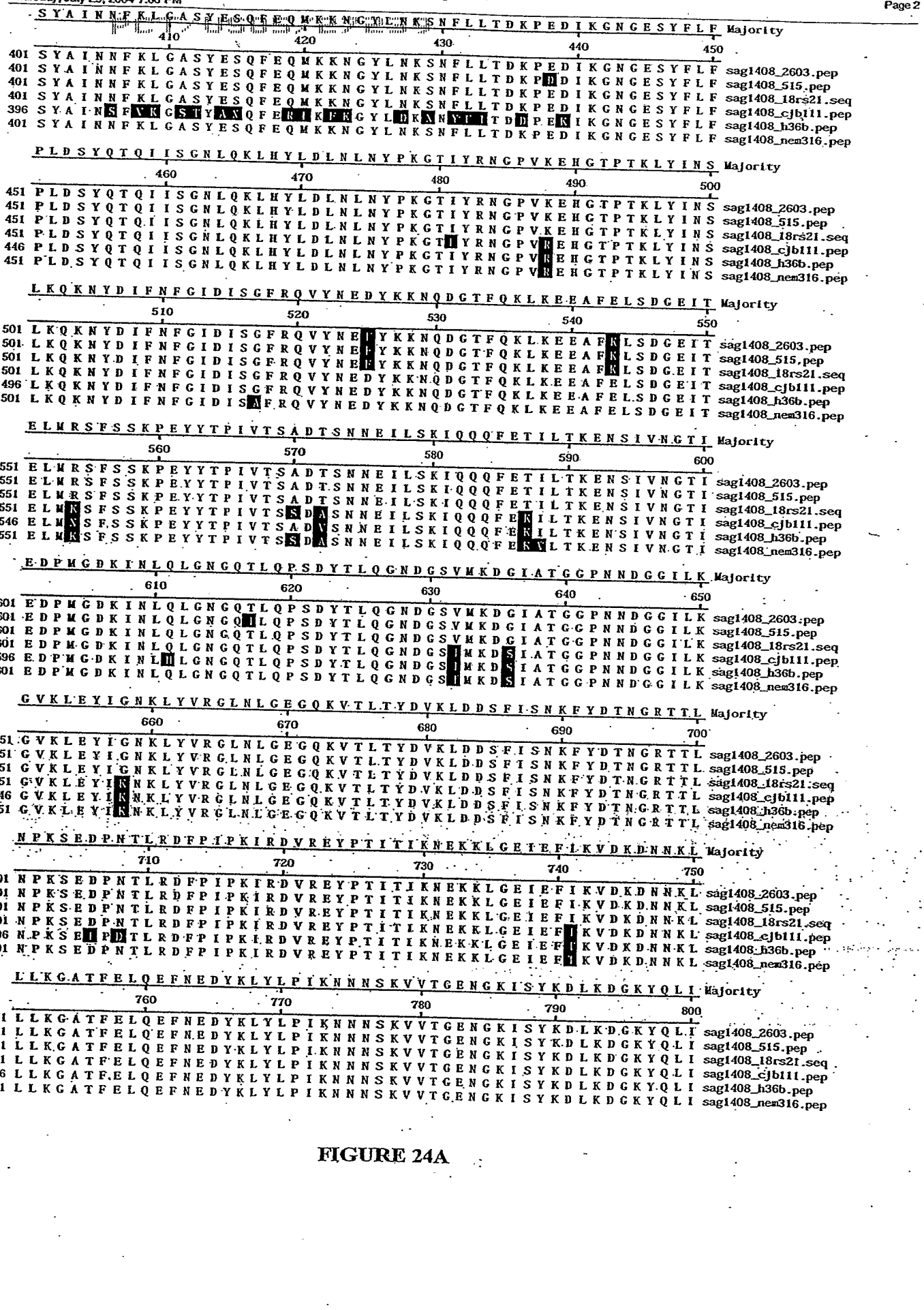

Figure 24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410 420 430 440 450
401 SYAINNFKLGASYESQFEQMKKNGYLNKSNFLLTDKPEDIKGNGESYFLF sag1408_2603.pep
401 SYAINNFKLGASYESQFEQMKKNGYLNKSNFLLTDKPDDIKGNGESYFLF sag1408_515.pep
401 SYAINNFKLGASYESQFEQMKKNGYLNKSNFLLTDKPEDIKGNGESYFLF sag1408_18rs21.seq
396 SYAINSFVKGSTYANQFERIKPFRGYLDKANYTITDDPEKIKGNGESYFLF sag1408_cjb111.pep
401 SYAINNFKLGASYESQFEQMKKNGYLNKSNFLLTDKPEDIKGNGESYFLF sag1408_h36b.pep
401 SYAINNFKLGASYESQFEQMKKNGYLNKSNFLLTDKPEDIKGNGESYFLF sag1408_nem316.pep
PLDSYQTQIISGNLQKLHYLDLNLNYPKGTIYRNGPVKEHGTPTKLYINS Majority
460 470 480 490 500
451 PLDSYQTQIISGNLQKLHYLDLNLNYPKGTIYRNGPVKEHGTPTKLYINS sag1408_2603.pep
451 PLDSYQTQIISGNLQKLHYLDLNLNYPKGTIYRNGPVKEHGTPTKLYINS sag1408_515.pep
451 PLDSYQTQIISGNLQKLHYLDLNLNYPKGTIYRNGPVKEHGTPTKLYINS sag1408_18rs21.seq
446 PLDSYQTQIISGNLQKLHYLDLNLNYPKGTIYRNGPVREHGTPTKLYINS sag1408_cjb111.pep
451 PLDSYQTQIISGNLQKLHYLDLNLNYPKGTIYRNGPVREHGTPTKLYINS sag1408_h36b.pep
451 PLDSYQTQIISGNLQKLHYLDLNLNYPKGTIYRNGPVREHGTPTKLYINS sag1408_nem316.pep
LKQKNYDIFNFGIDISGFRQVYNEDYKKNQDGTFQKLKEEAFELSDGEIT Majority
510 520 530 540 550
501 LKQKNYDIFNFGIDISGFRQVYNEIYKKNQDGTFQKLKEEAFKLSDGEIT sag1408_2603.pep
501 LKQKNYDIFNFGIDISGFRQVYNEIYKKNQDGTFQKLKEEAFKLSDGEIT sag1408_515.pep
501 LKQKNYDIFNFGIDISGFRQVYNEIYKKNQDGTFQKLKEEAFKLSDGEIT sag1408_18rs21.seq
496 LKQKNYDIFNFGIDISGFRQVYNEDYKKNQDGTFQKLKEEAFELSDGEIT sag1408_cjb111.pep
501 LKQKNYDIFNFGIDISAFRQVYNEDYKKNQDGTFQKLKEEAFELSDGEIT sag1408_h36b.pep
501 LKQKNYDIFNFGIDISGFRQVYNEDYKKNQDGTFQKLKEEAFELSDGEIT sag1408_nem316.pep
ELMRSFSSKPEYYTPIVTSADTSNNEILSKIQQQFETILTKENSIVNGTI Majority
560 570 580 590 600
551 ELMRSFSSKPEYYTPIVTSADTSNNEILSKIQQQFETILTKENSIVNGTI sag1408_2603.pep
551 ELMRSFSSKPEYYTPIVTSADTSNNEILSKIQQQFETILTKENSIVNGTI sag1408_515.pep
551 ELMKSFSSKPEYYTPIVTSSDASNNEILSKIQQQFENILTKENSIVNGTI sag1408_18rs21.seq
546 ELMNSFSSKPEYYTPIVTSADVSNNEILSKIQQQFENILTKENSIVNGTI sag1408_cjb111.pep
551 ELMKSFSSKPEYYTPIVTSSDASNNEILSKIQQQFEKVLTKENSIVNGTI sag1408_h36b.pep
551 ELMKSFSSKPEYYTPIVTSSDASNNEILSKIQQQFEKVLTKENSIVNGTI sag1408_nem316.pep
EDPMGDKINLQLGNGQTLQPSDYTLQGNDGSVMKDGIATGGPNNDGGILK Majority
610 620 630 640 650
601 EDPMGDKINLQLGNGQILQPSDYTLQGNDGSVMKDGIATGGPNNDGGILK sag1408_2603.pep
601 EDPMGDKINLQLGNGQTLQPSDYTLQGNDGSVMKDGIATGGPNNDGGILK sag1408_515.pep
601 EDPMGDKINLQLGNGQTLQPSDYTLQGNDGSIMKDGIATGGPNNDGGILK sag1408_18rs21.seq
596 EDPMGDKINLHLGNGQTLQPSDYTLQGNDGSIMKDSIATGGPNNDGGILK sag1408_cjb111.pep
601 EDPMGDKINLQLGNGQTLQPSDYTLQGNDGSIMKDSIATGGPNNDGGILK sag1408_h36b.pep
601 EDPMGDKINLQLGNGQTLQPSDYTLQGNDGSIMKDSIATGGPNNDGGILK sag1408_nem316.pep
GVKLEYIGNKLYVRGLNLGEGQKVTLTYDVKLDDSFISNKFYDTNGRTTL Majority
660 670 680 690 700
651 GVKLEYIGNKLYVRGLNLGEGQKVTLTYDVKLDDSFISNKFYDTNGRTTL sag1408_2603.pep
651 GVKLEYIGNKLYVRGLNLGEGQKVTLTYDVKLDDSFISNKFYDTNGRTTL sag1408_515.pep
651 GVKLEYIKNKLYVRGLNLGEGQKVTLTYDVKLDDSFISNKFYDTNGRTTL sag1408_18rs21.seq
646 GVKLEYIKNKLYVRGLNLGEGQKVTLTYDVKLDDSFISNKFYDTNGRTTL sag1408_cjb111.pep
651 GVKLEYIKNKLYVRGLNLGEGQKVTLTYDVKLDDSFISNKFYDTNGRTTL sag1408_h36b.pep
651 GVKLEYIKNKLYVRGLNLGEGQKVTLTYDVKLDDSFISNKFYDTNGRTTL sag1408_nem316.pep
NPKSEDPNTLRDFPIPKIRDVREYPTITIKNEKKLGETEFIKVDKDNNKL Majority
710 720 730 740 750
701 NPKSEDPNTLRDFPIPKIRDVREYPTITIKNEKKLGEIEFIKVDKDNNKL sag1408_2603.pep
701 NPKSEDPNTLRDFPIPKIRDVREYPTITIKNEKKLGEIEFIKVDKDNNKL sag1408_515.pep
701 NPKSEDPNTLRDFPIPKIRDVREYPTITIKNEKKLGEIEFIKVDKDNNKL sag1408_18rs21.seq
696 NPKSEIPDTLRDFPIPKIRDVREYPTITIKNEKKLGEIEFIKVDKDNNKL sag1408_cjb111.pep
701 NPKSEDPNTLRDFPIPKIRDVREYPTITIKNEKKLGEIEFIKVDKDNNKL sag1408_h36b.pep
701 NPKSEDPNTLRDFPIPKIRDVREYPTITIKNEKKLGEIEFIKVDKDNNKL sag1408_nem316.pep
LLKGATFELQEFNEDYKLYLPIKNNNSKVVTGENGKISYKDLKDGKYQLI Majority
760 770 780 790 800
751 LLKGATFELQEFNEDYKLYLPIKNNNSKVVTGENGKISYKDLKDGKYQLI sag1408_2603.pep
751 LLKGATFELQEFNEDYKLYLPIKNNNSKVVTGENGKISYKDLKDGKYQLI sag1408_515.pep
751 LLKGATFELQEFNEDYKLYLPIKNNNSKVVTGENGKISYKDLKDGKYQLI sag1408_18rs21.seq
746 LLKGATFELQEFNEDYKLYLPIKNNNSKVVTGENGKISYKDLKDGKYQLI sag1408_cjb111.pep
751 LLKGATFELQEFNEDYKLYLPIKNNNSKVVTGENGKISYKDLKDGKYQLI sag1408_h36b.pep
751 LLKGATFELQEFNEDYKLYLPIKNNNSKVVTGENGKISYKDLKDGKYQLI sag1408_nem316.pep

FIGURE 24A

```
    E A V S P E D Y Q K I T N K P I L T F E V V K G S I K N I I A V N K Q I S E Y H E E G D K H L I T N Majority
                                 810       820       830       840       850
801 E A V S P E D Y Q K I T N K P I L T F E V V K G S I K N I I A V N K Q I S E Y H E E G D K H L I T N sag1408_2603.pep
801 E A V S P E D Y Q K I T N K P I L T F E V V K G S I K N I I A V N K Q I S E Y H E E G D K H L I T N sag1408_515.pep
801 E A V S P E D Y Q K I T N K P I L T F E V V K G S I K N I I A V N K Q I S E Y H E E G D K H L I T N sag1408_18rs21.seq
801 E A V S P K D Y Q K I T N K P I L T F E V V K G S I Q N I I A V N K Q I S E Y H E E G D K H L I T N sag1408_cjb111.pep
796 E A V S P K D Y Q K I T N K P I L T F E V V K G S I Q N I I A V N K Q I S E Y H E E G D K H L I T N sag1408_h36b.pep
801 E A V S P K D Y Q K I T N K P I L T F E V V K G S I Q N I I A V N K Q I S E Y H E E G D K H L I T N sag1408_nem316.pep

    T H I P P K G I I P M T G G K G I L S F I L I G G A M M S I A G G I Y I W K R Y K K S S D M S I E K Majority
                                 860       870       880       890       900
851 T H I P P K G I I P M T G G K G I L S F I L I G G A M M S I A G G I Y I W K R Y K K S S D M S I K K sag1408_2603.pep
851 T H I P P K G I I P K T G G K G I L S F I L I G G A M M S I A G G I Y I W K R Y K K S S D M S I K K sag1408_515.pep
851 T H I P P K G I I P M T G G K G I L S F I L I G G A M M S I A G G I Y I W K R Y K K S S D M S I K K sag1408_18rs21.seq
851 T H I P P K G I I P M T G G K G I L S F I L I G G S M M S I A G G I Y I W K R Y K K S S D I S R E K sag1408_cjb111.pep
846 T H I P P K G I I P M T G G K G I L S F I L I G G A M M S I A G G I Y I W K R H K K S S D A S I E K sag1408_h36b.pep
851 T H I P P K G I I P M T G G K G I L S F I L I G G S M M S I A G G I Y I W K R Y K K S S D I S R E K sag1408_nem316.pep

    D                                                                                           Majority
901 D
901 D                                                                                           sag1408_2603.pep
901 D                                                                                           sag1408_515.pep
901 D                                                                                           sag1408_18rs21.seq
896 D                                                                                           sag1408_cjb111.pep
901 D                                                                                           sag1408_h36b.pep
                                                                                                sag1408_nem316.pep
```

Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

FIGURE 24B

Figure 25: GBS closely associate with tight junctions and cross the monolayer by a paracellular route

Transmission Electron Microscopy images of GBS infection of ME180 cervical epithelial cells.

Figure 26: GBS infection of ME180 cells
GBS infection of ME180 cells

Figure 27

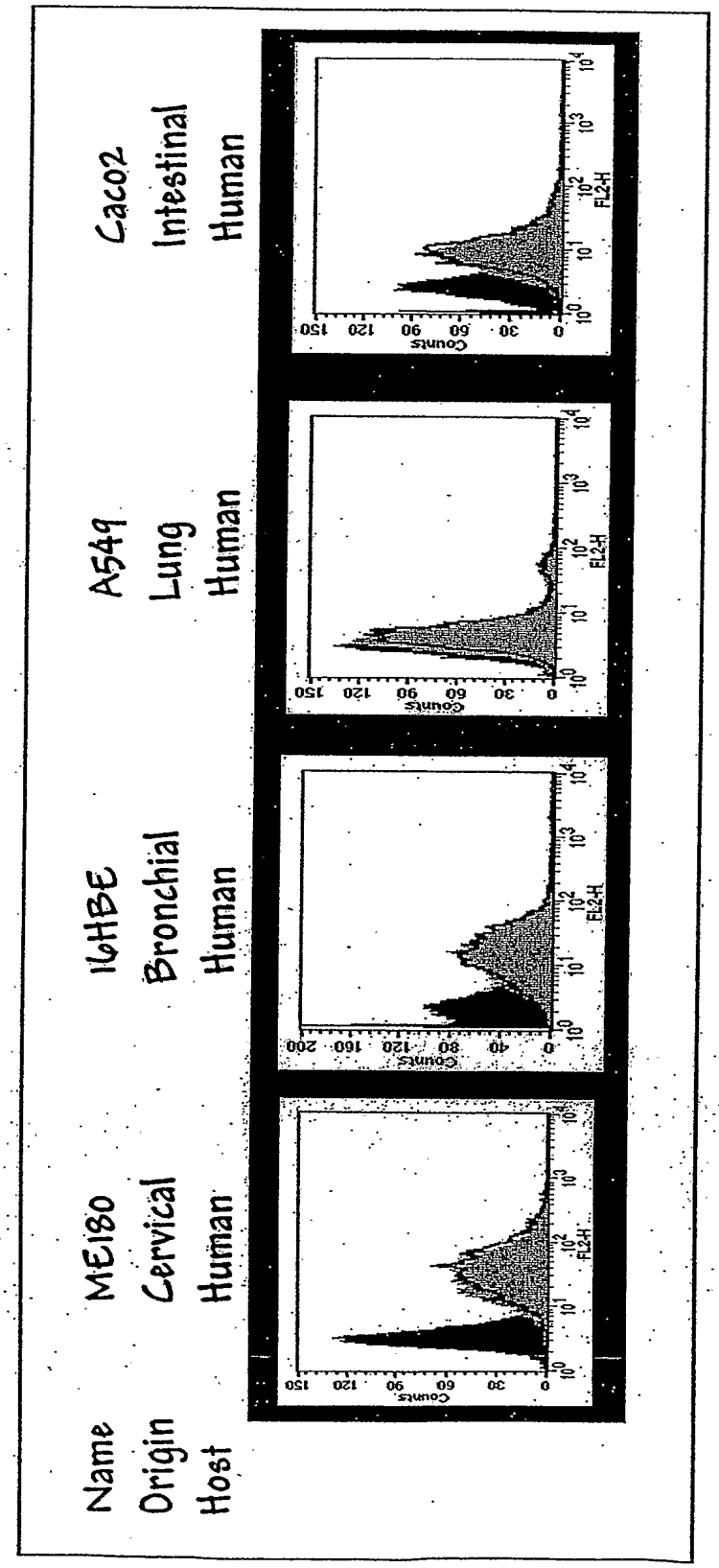
Name
Origin
Host
ME180
Cervical
Human
16HBE
Bronchial
Human
A549
Lung
Human
Caco2
Intestinal
Human
Counts
FL2-H

Figure 28

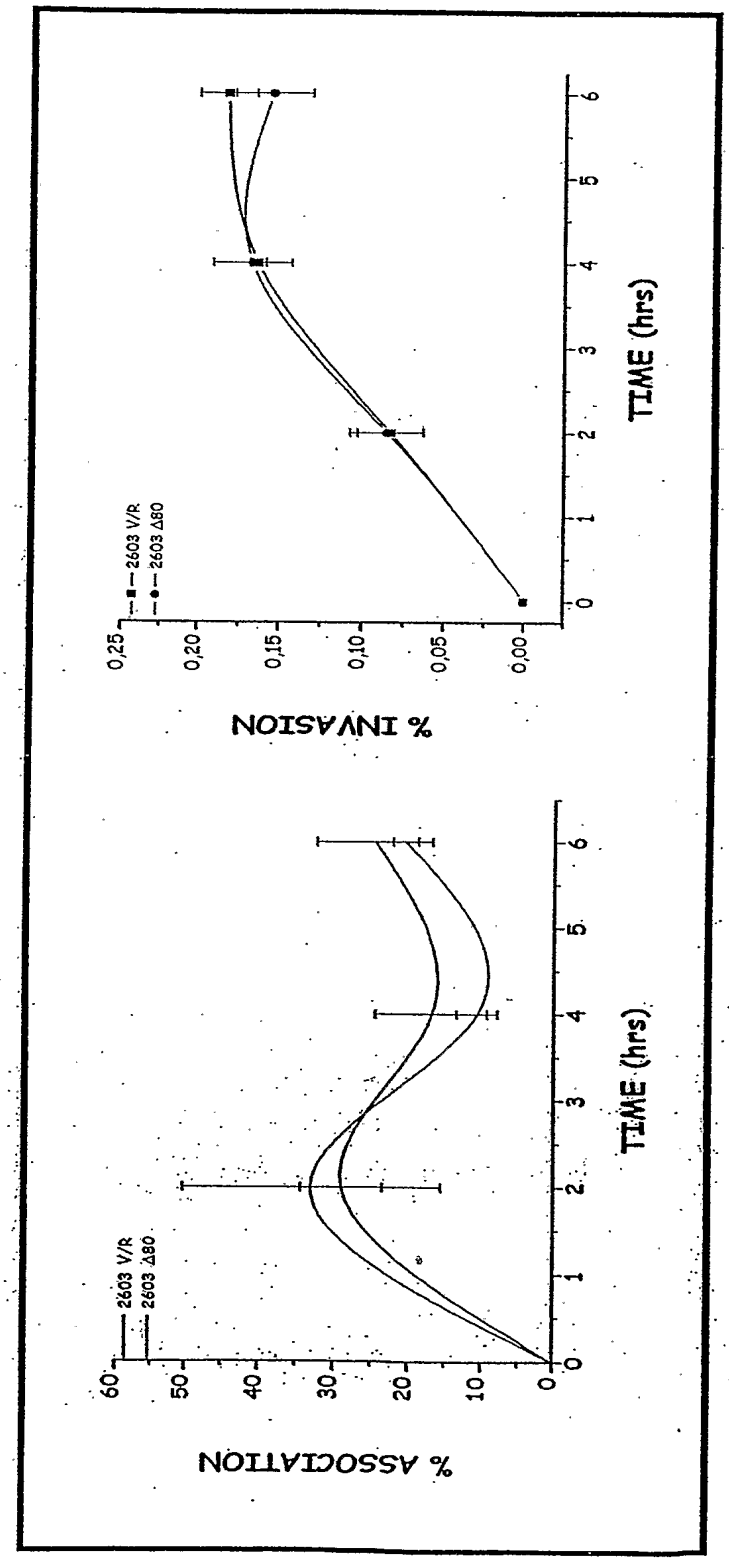
% ASSOCIATION
TIME (hrs)
2603 V/R
2603 Δ80
% INVASION
TIME (hrs)
2603 V/R
2603 Δ80

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Figure 29

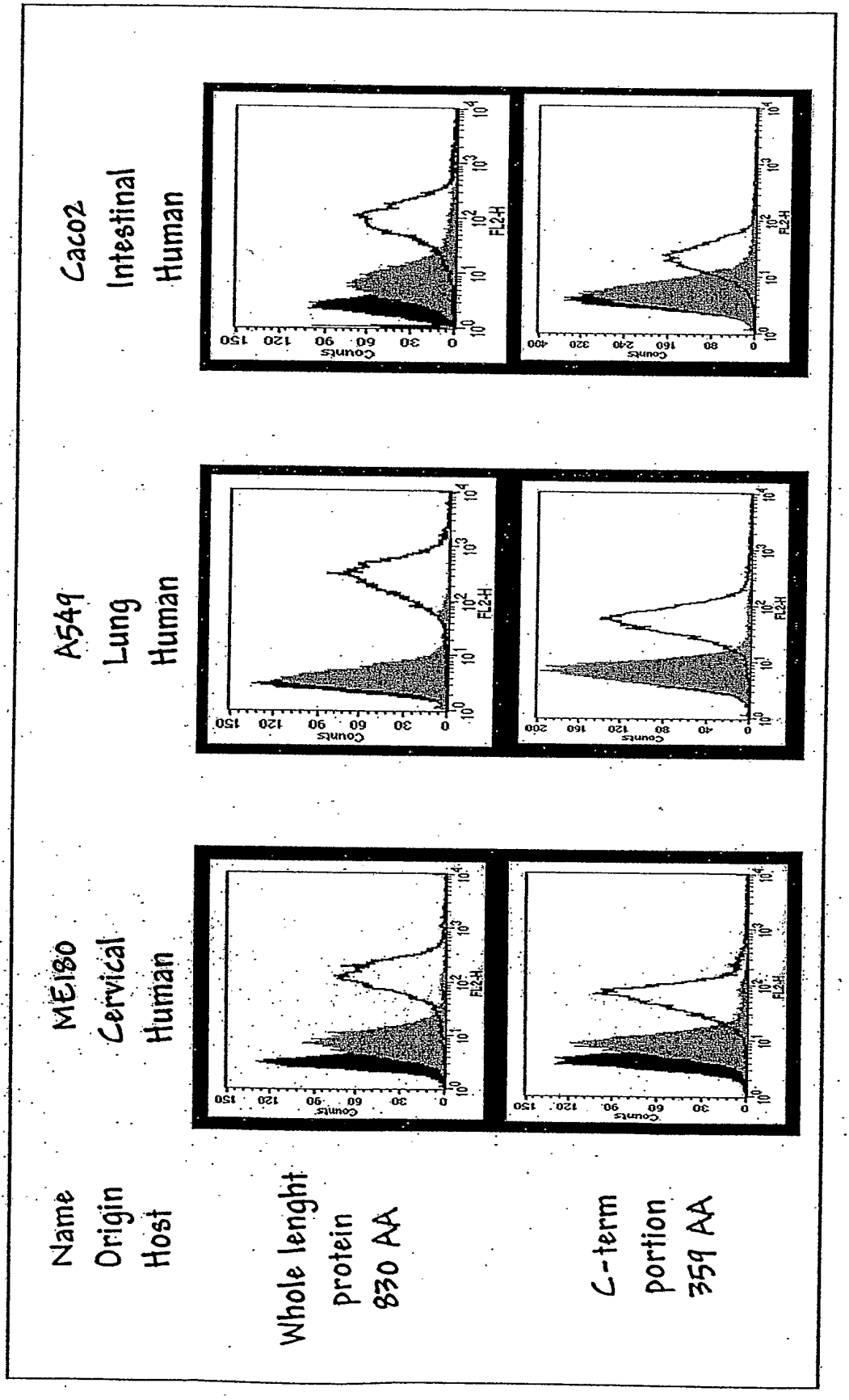

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Figure 30

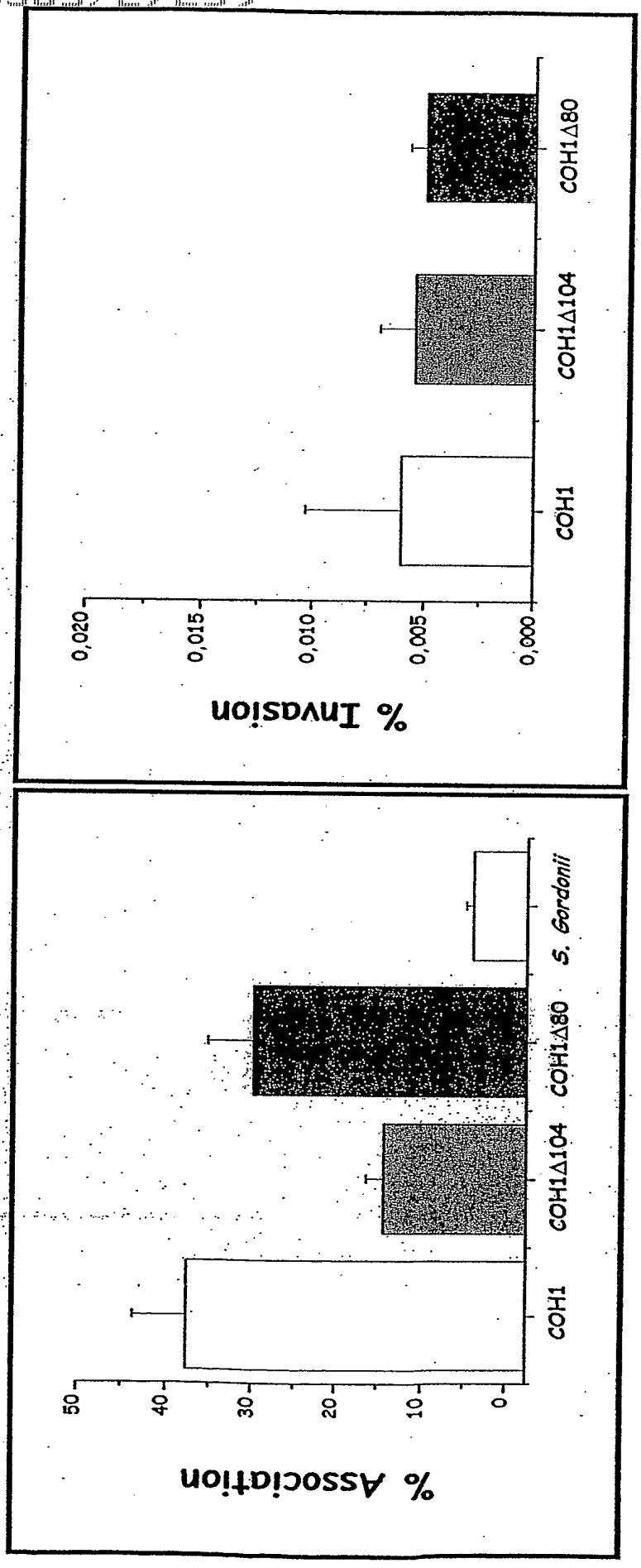

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Figure 31

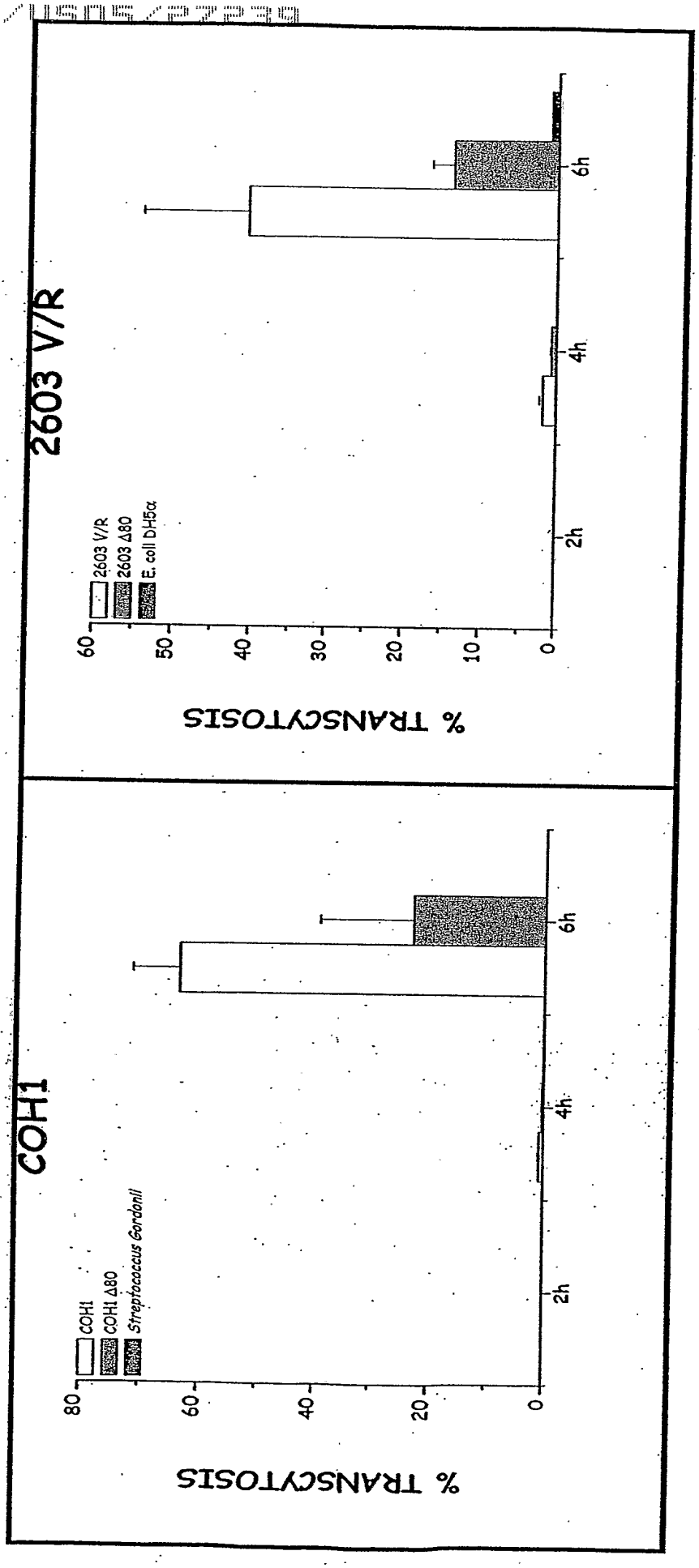

Figure 32

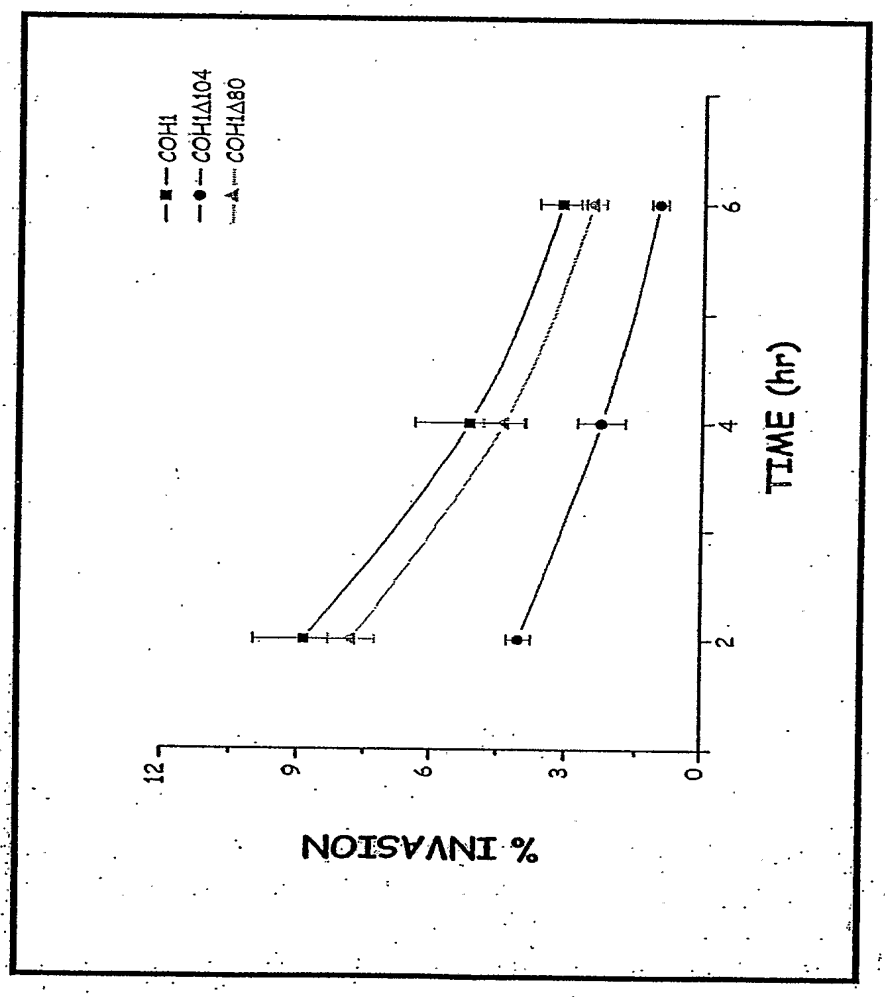

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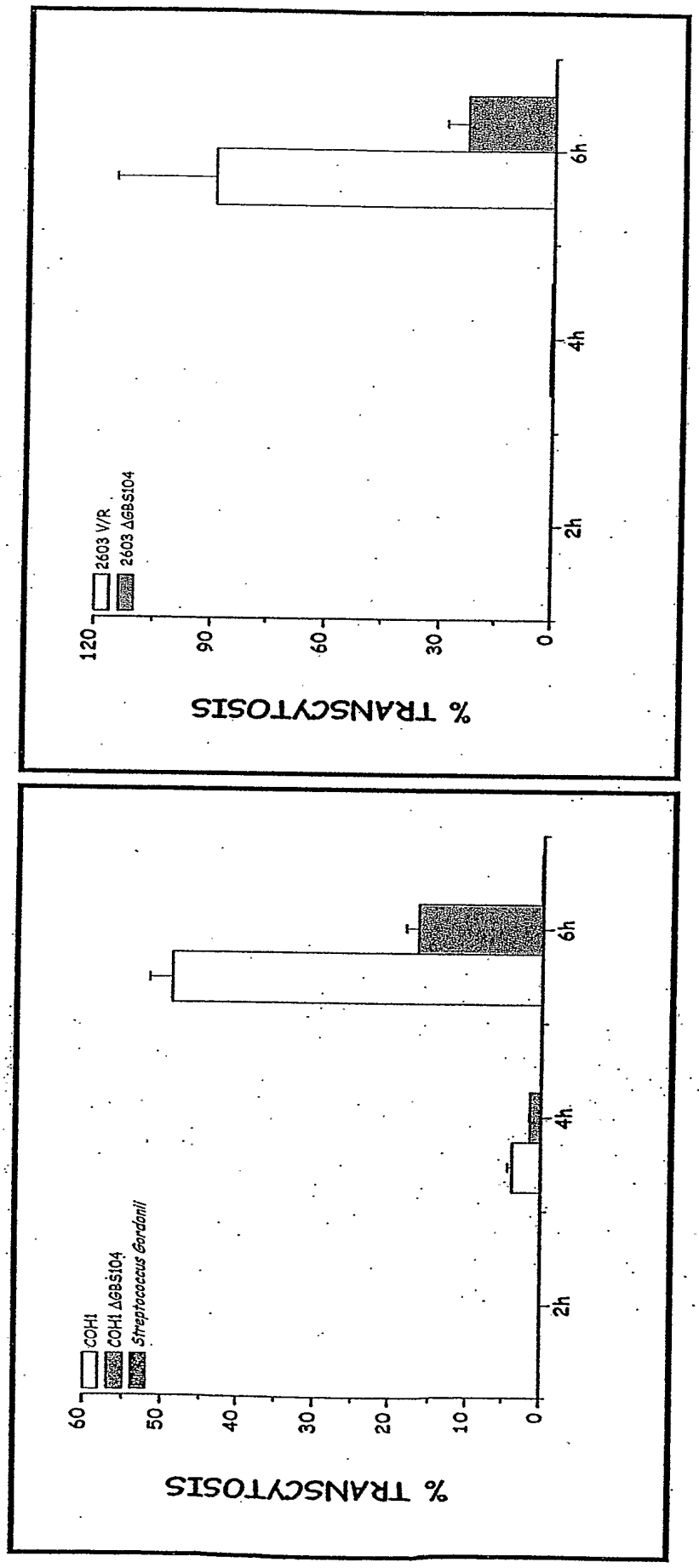
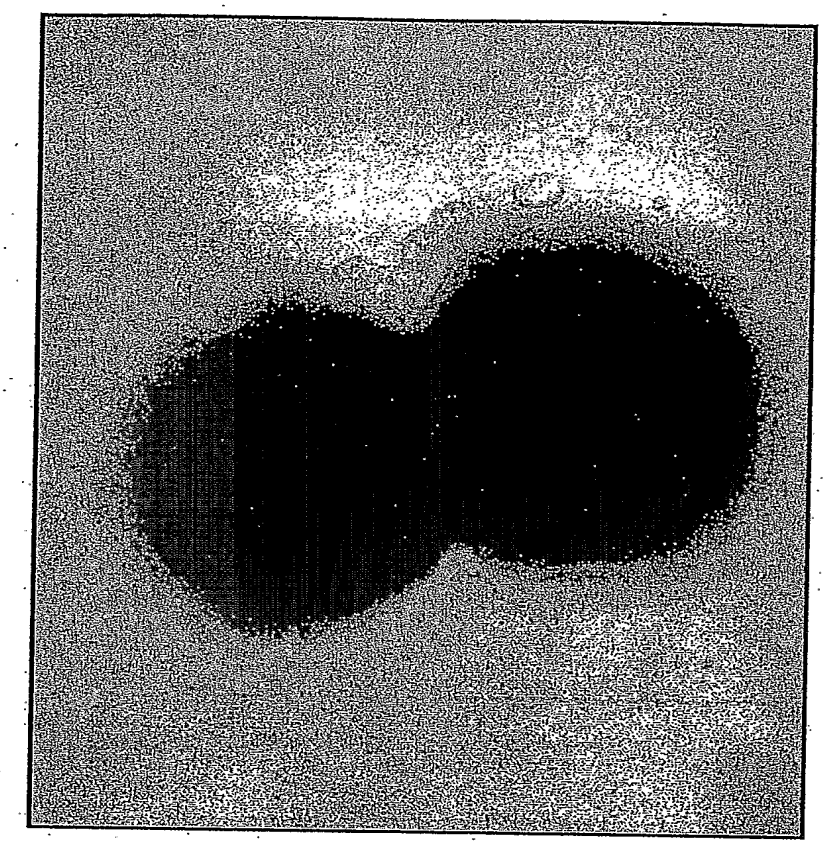
Figure 33



GBS STRAIN COH1 over GBS80

Negative staining EM



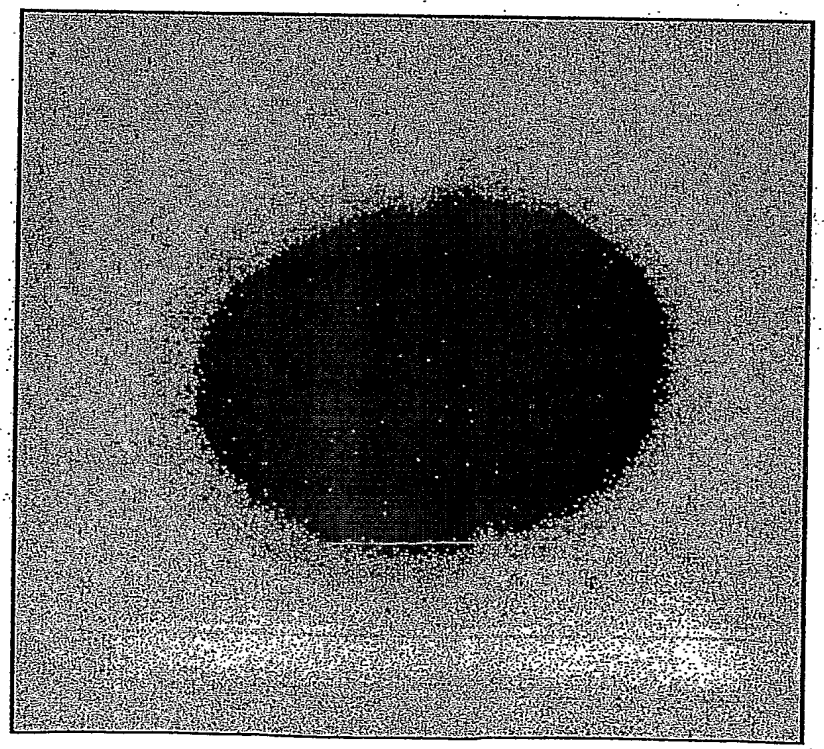


Figure 34

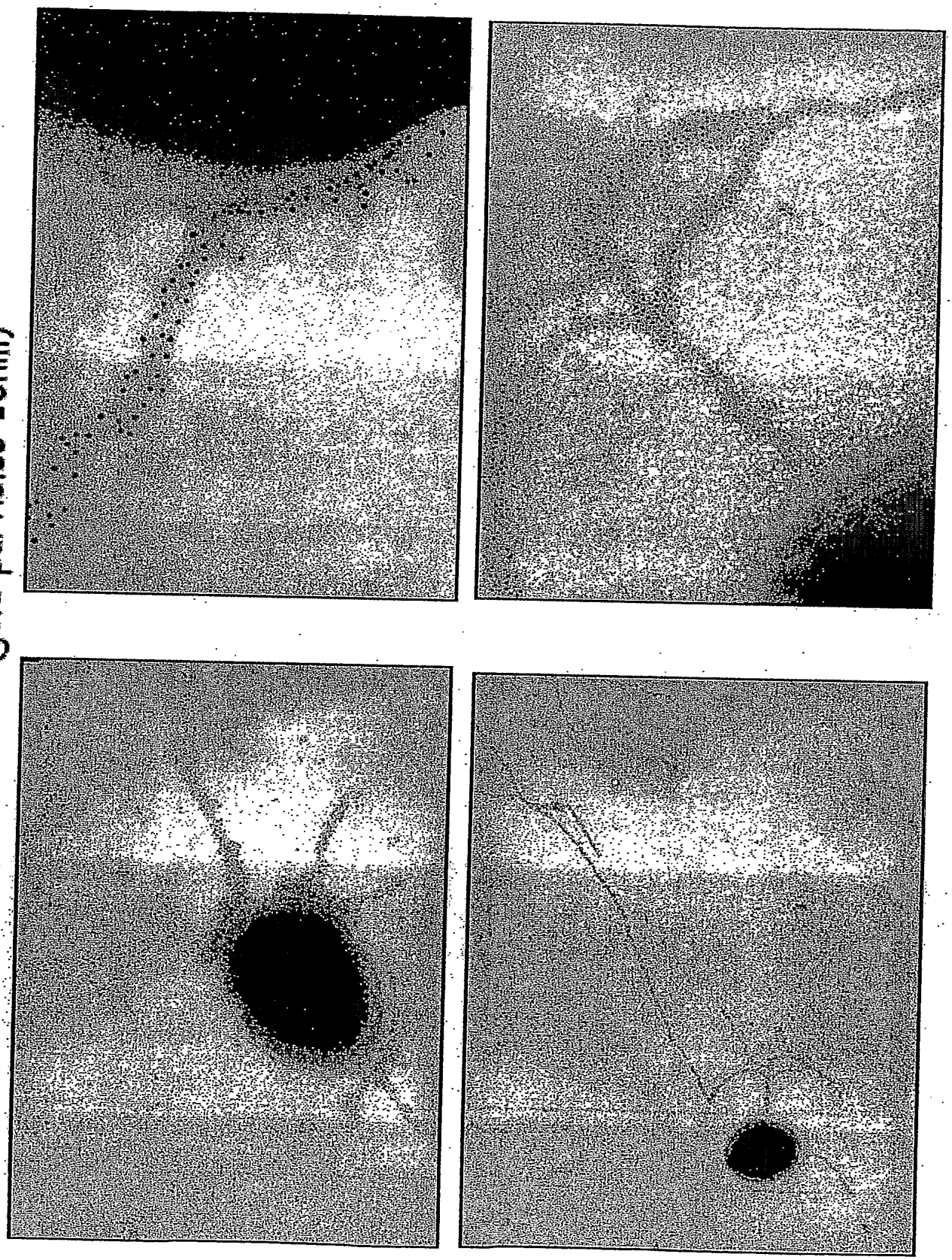

GBS STRAIN COH1 over GBS80
IEM anti-GBS80 (gold particles 10nm)

Figure 35

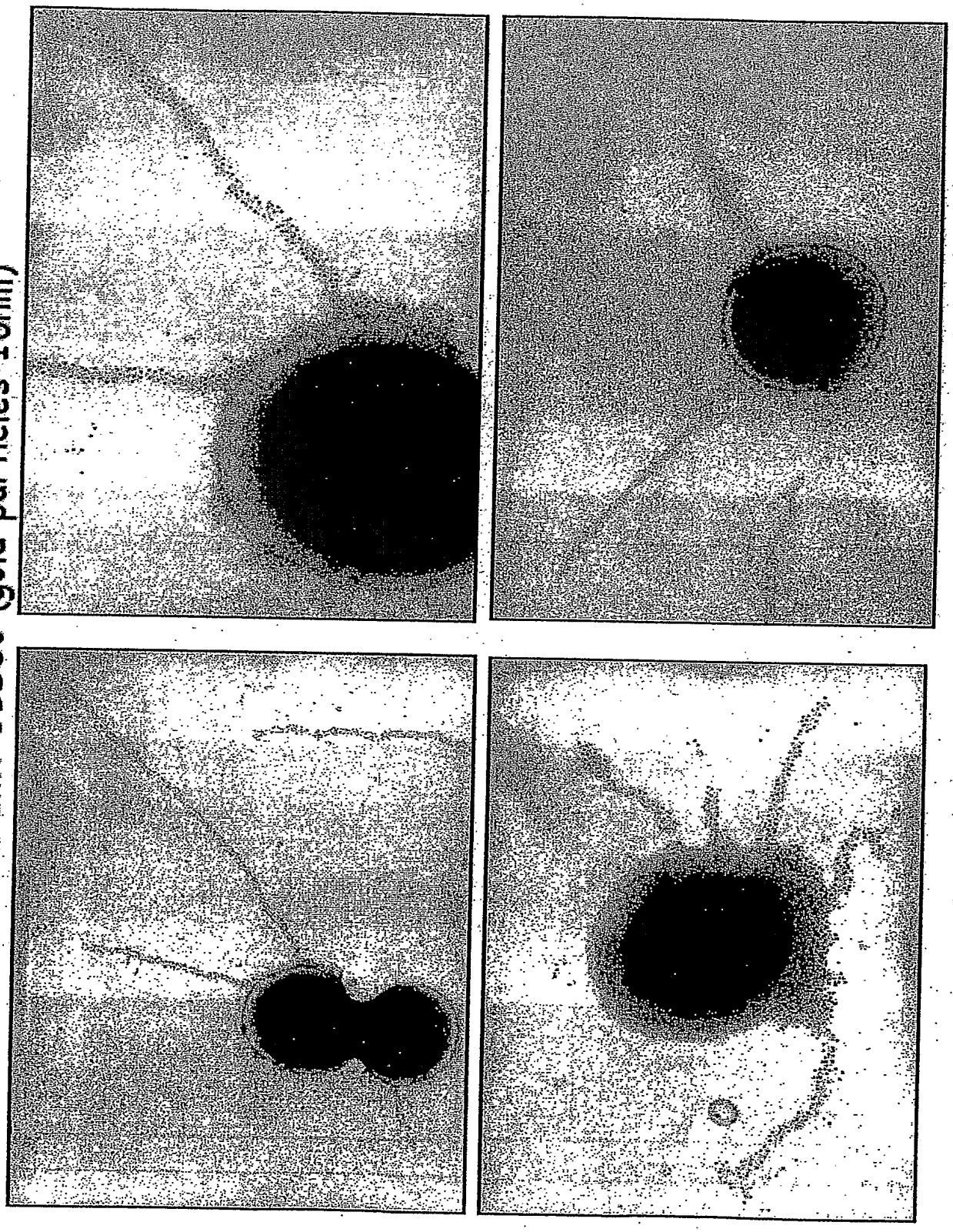

GBS STRAIN COH1 over GBS80
IEM anti-GBS80 (gold particles 10nm)

Figure 36

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GBS STRAIN COH1 over GBS80

IEM anti-GBS80 (gold particles 20nm)

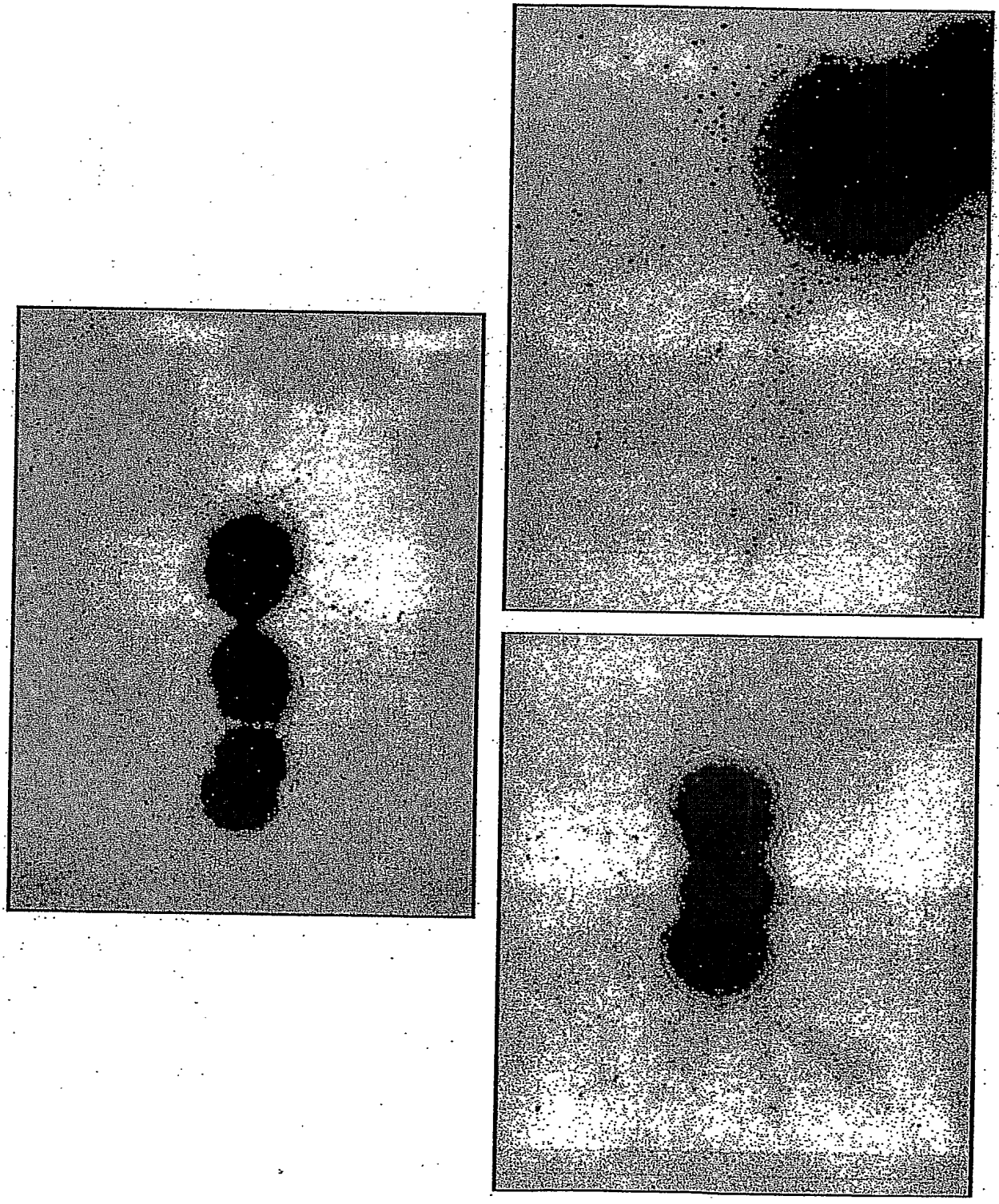

Figure 37

Figure 38

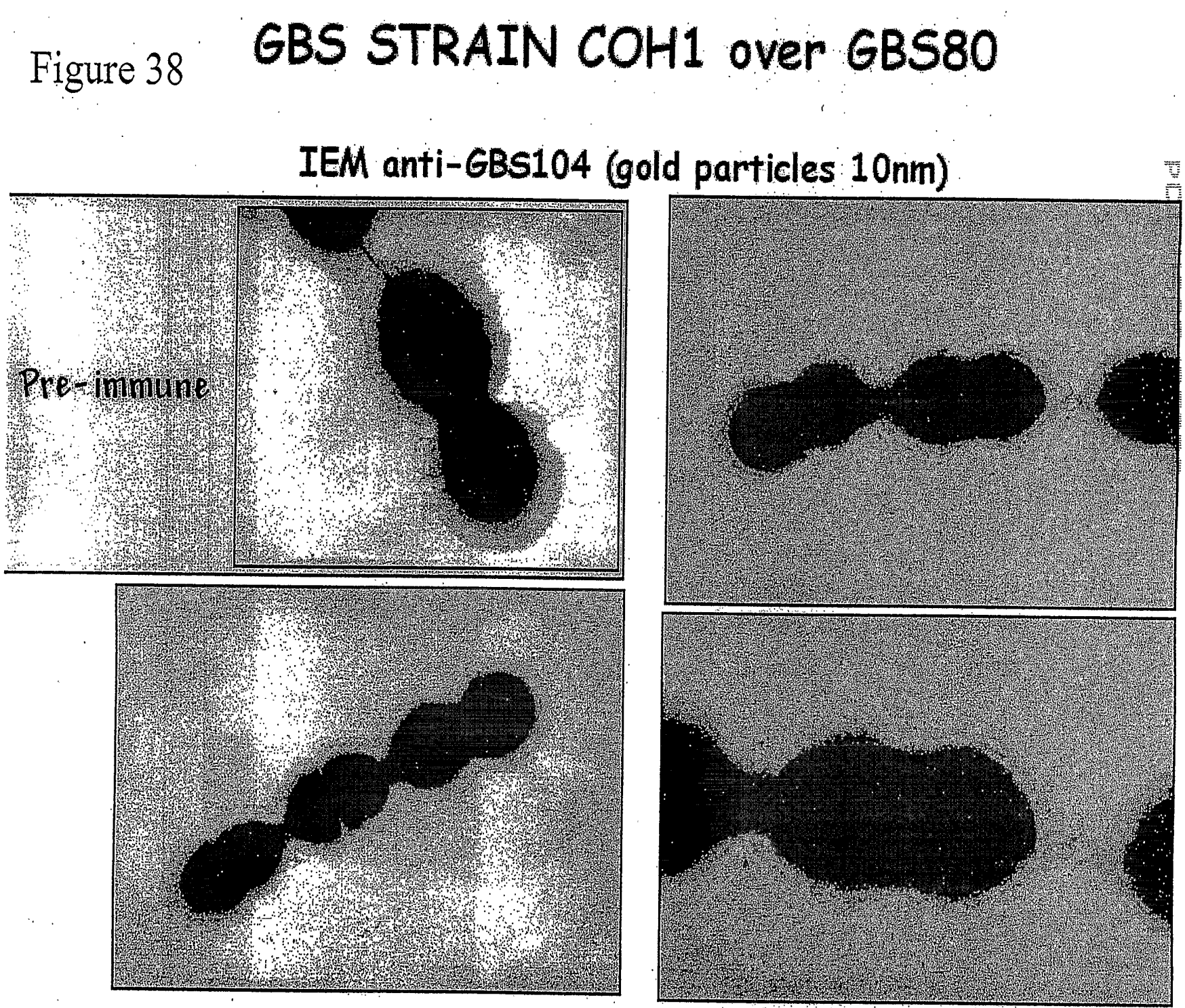
GBS STRAIN COH1 over GBS80
IEM anti-GBS104 (gold particles 10nm)
Pre-immune

Figure 39

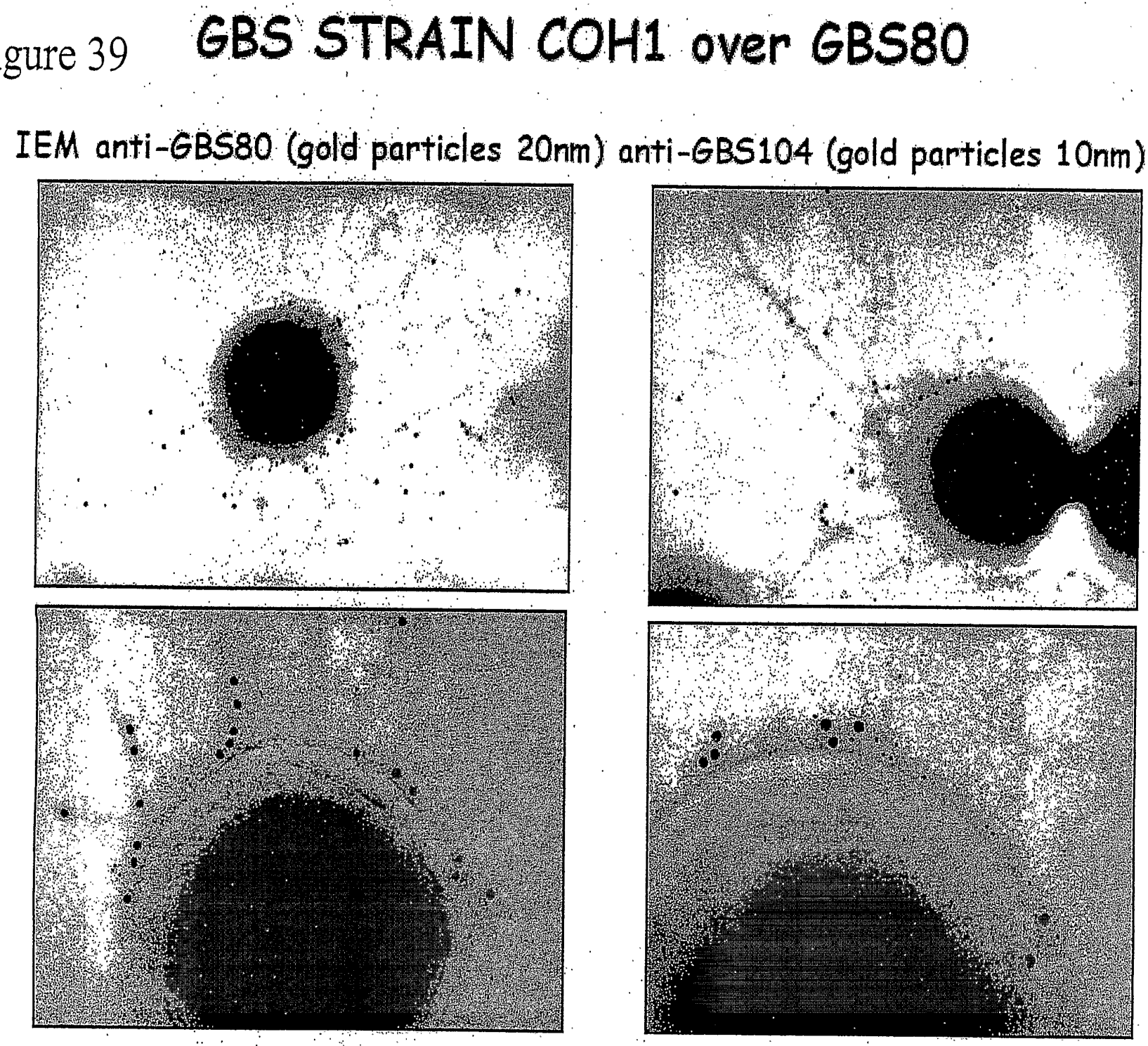

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Figure 40 GBS STRAIN COH1 over GBS80

IEM anti-GBS80 (gold particles 20nm) anti-GBS104 (gold particles 10nm)

Figure 41: GBS 80 is necessary for polymer formation, GBS104 and sortase SAG0648 are necessary for efficient assembly

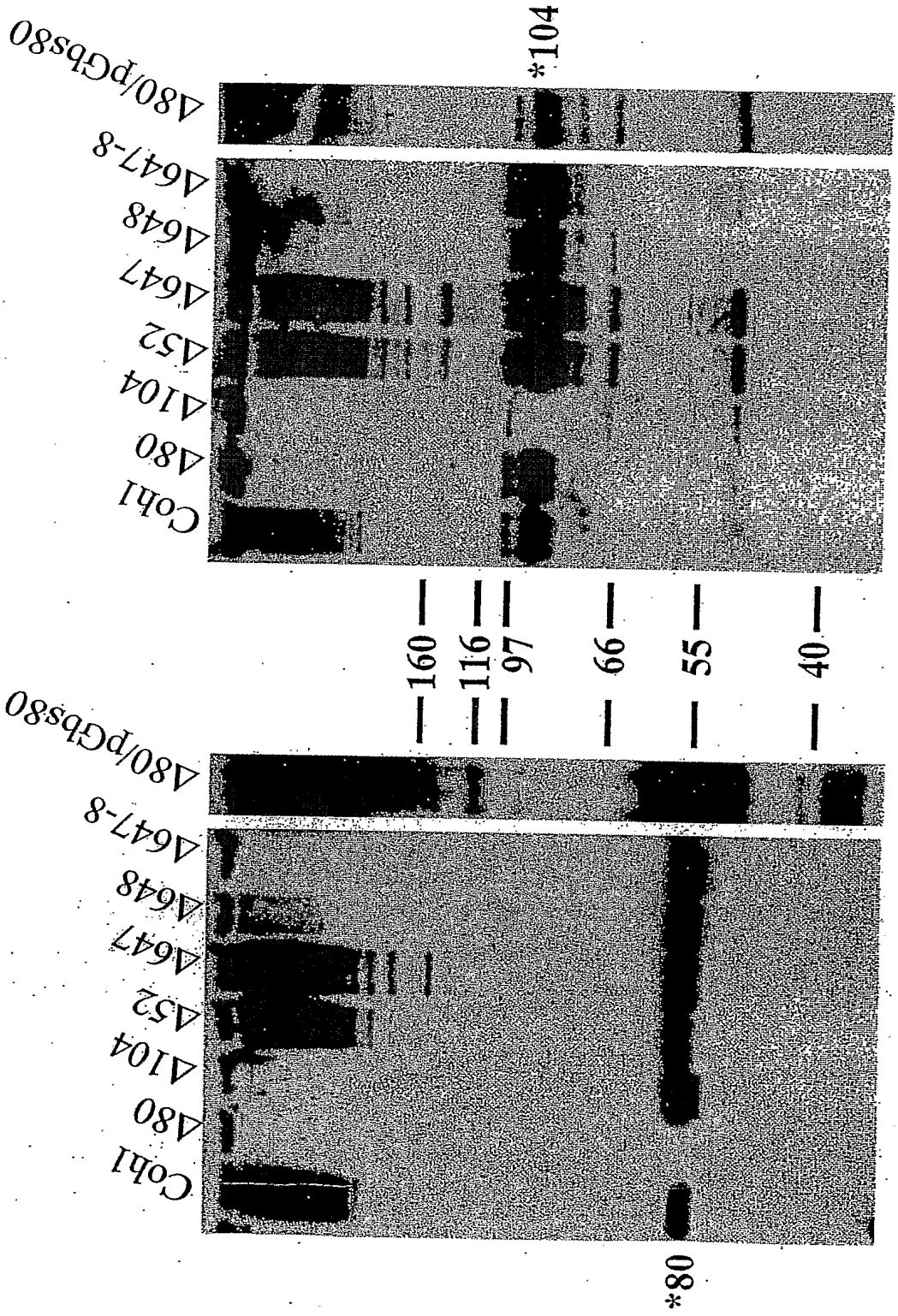
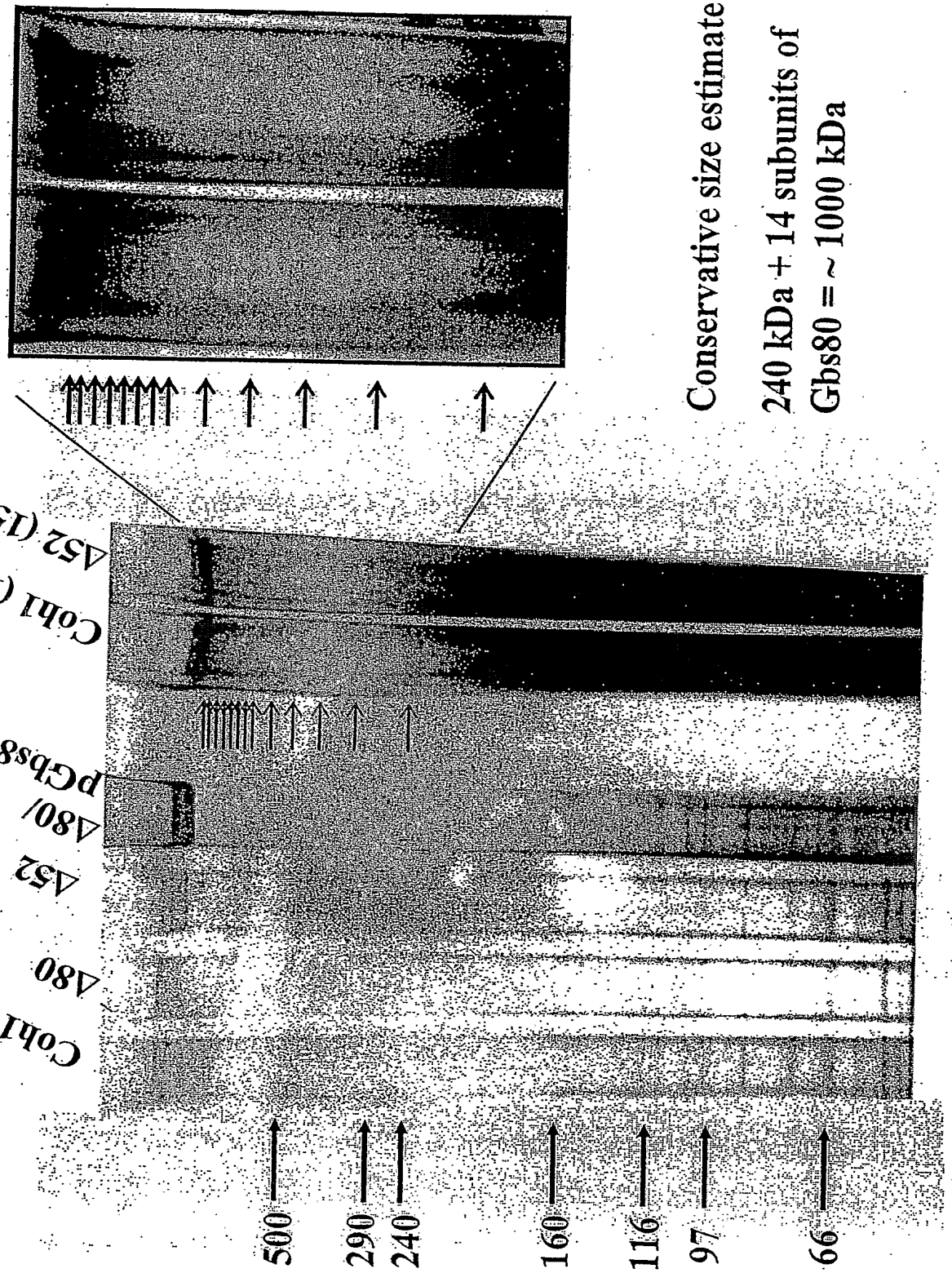


Figure 42: Gbs67 is part of a second pilus; Gbs80 is polymerized in strain 515

(515 lacks sortase 647-8, but has AI-2 sortases)

Figure 43: Two macro-molecules are visible in Cohl at >1000 kDa, one is the Gbs80 pilin



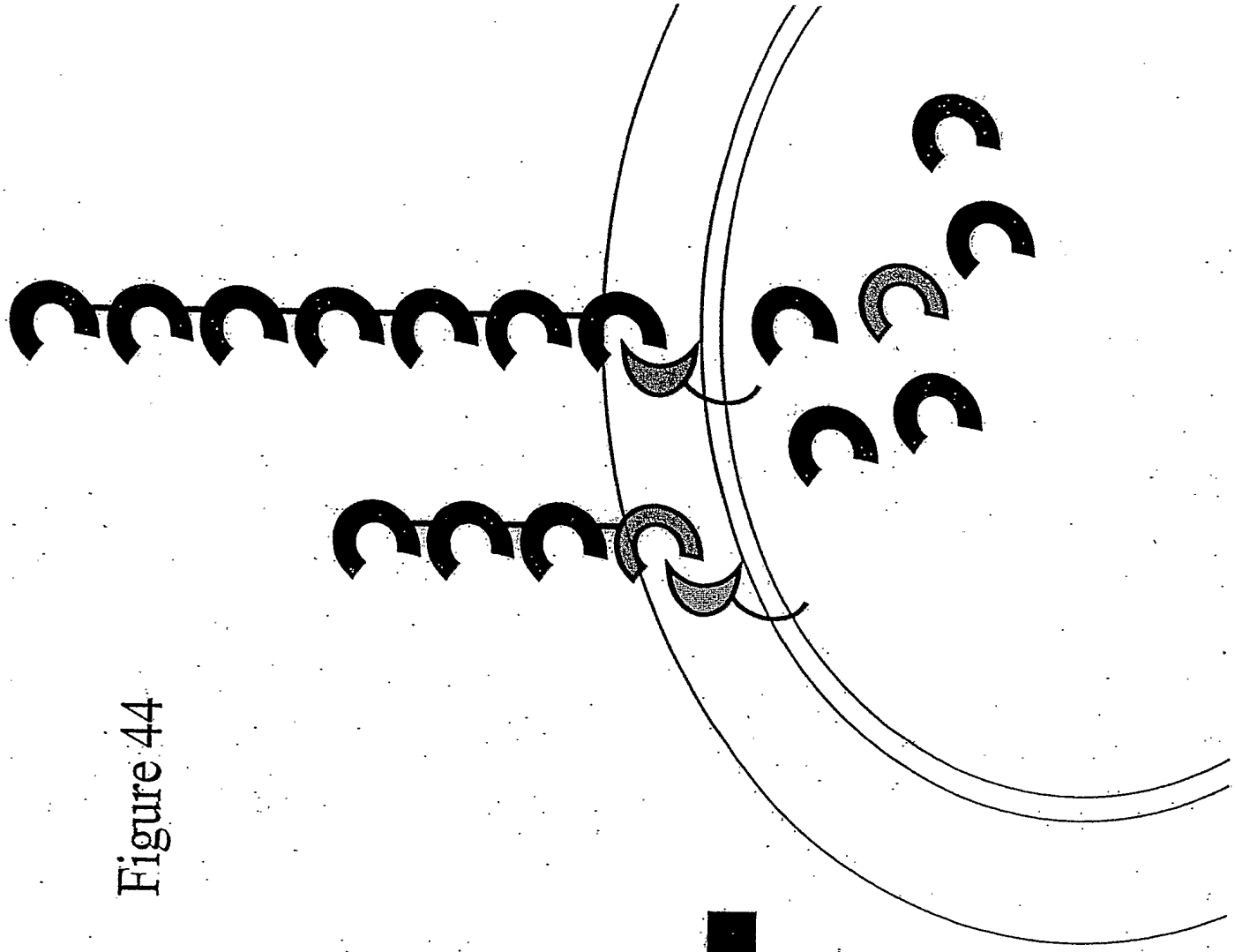


Figure 44

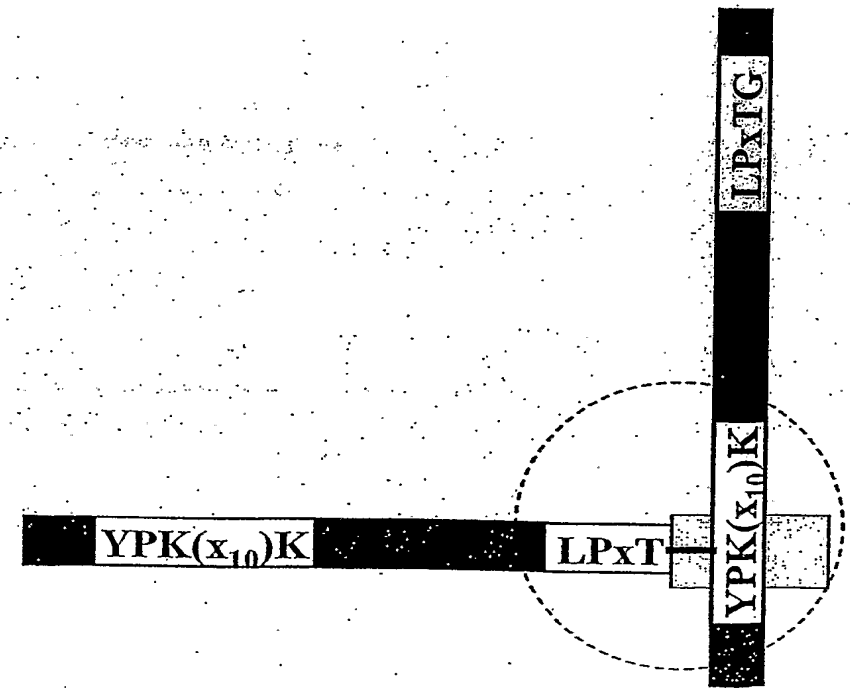
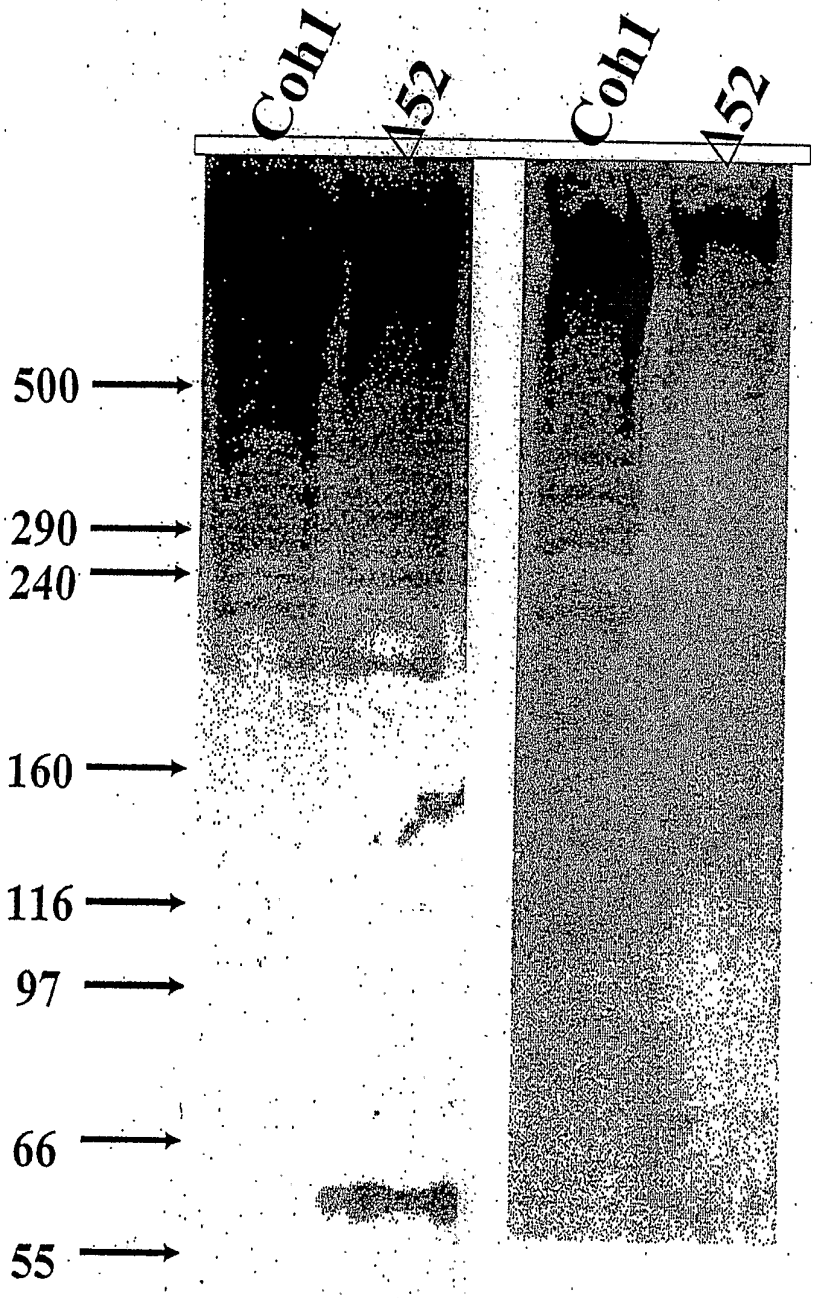


Figure 45: Gbs52 is a minor component of the GBS pilus



3%-8% Tris-acetate gels, includes stack

Left: α-gbs80

Right: blot stripped and reprobed with α-gbs52

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Figure 46: The pilus is found in the supernatant of the bacterial culture

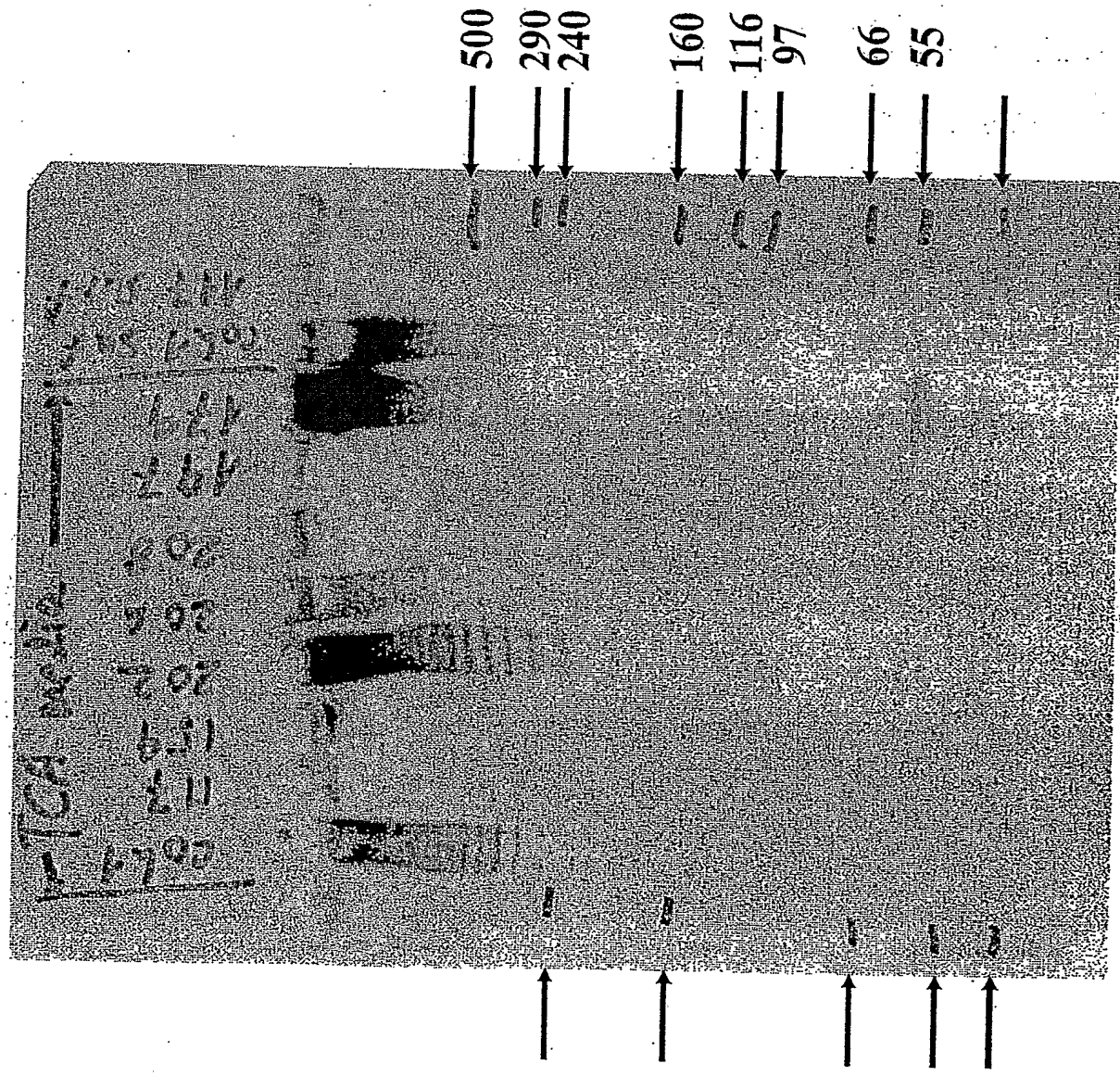
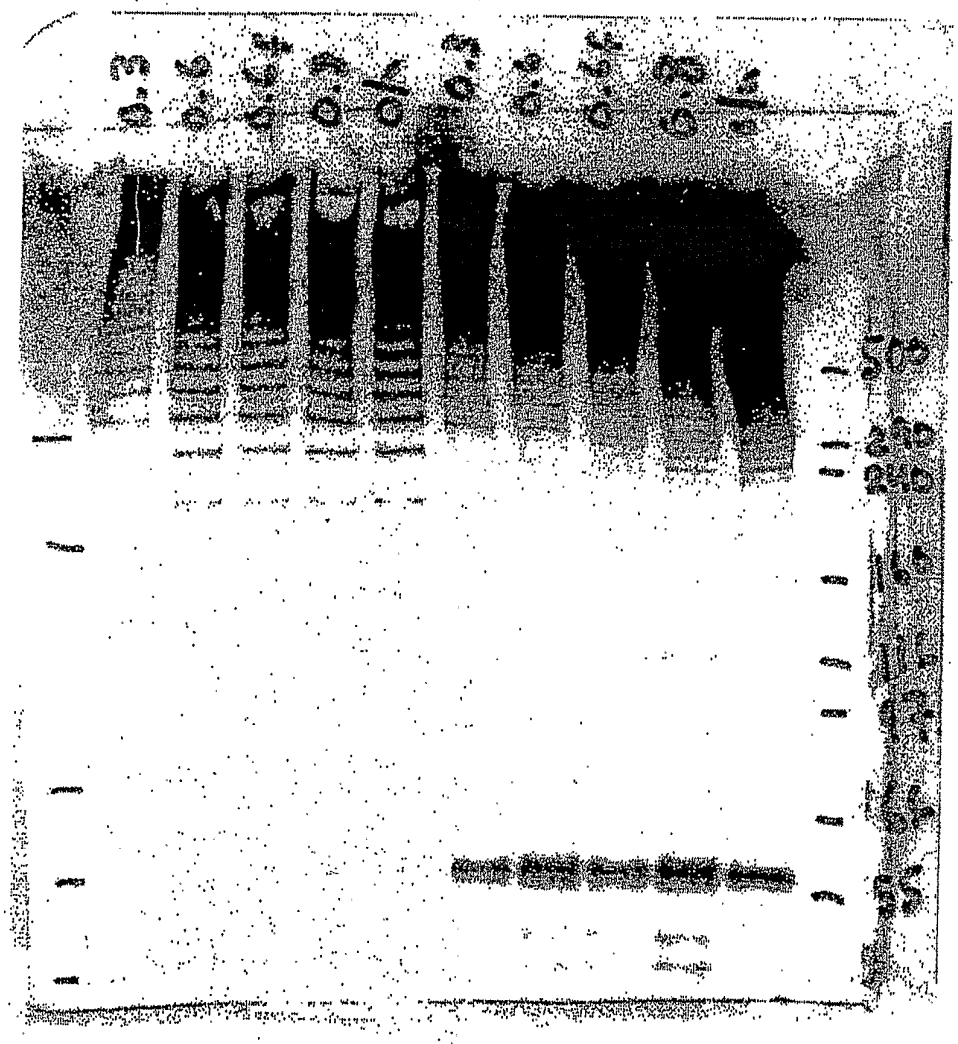


Figure 47: The pilus is found in the supernatant of cultures in all growth phases



TCA precipitation of 1 ml of THB culture supernatant run on 3-8% SDS-PAGE. OD600 nm are noted above samples, "f" indicates supernatant was filtered (0.2 μM syringe filter).

Left five samples: Coh1.

Right five samples: 179 (ΔGbs80/pGbs80).

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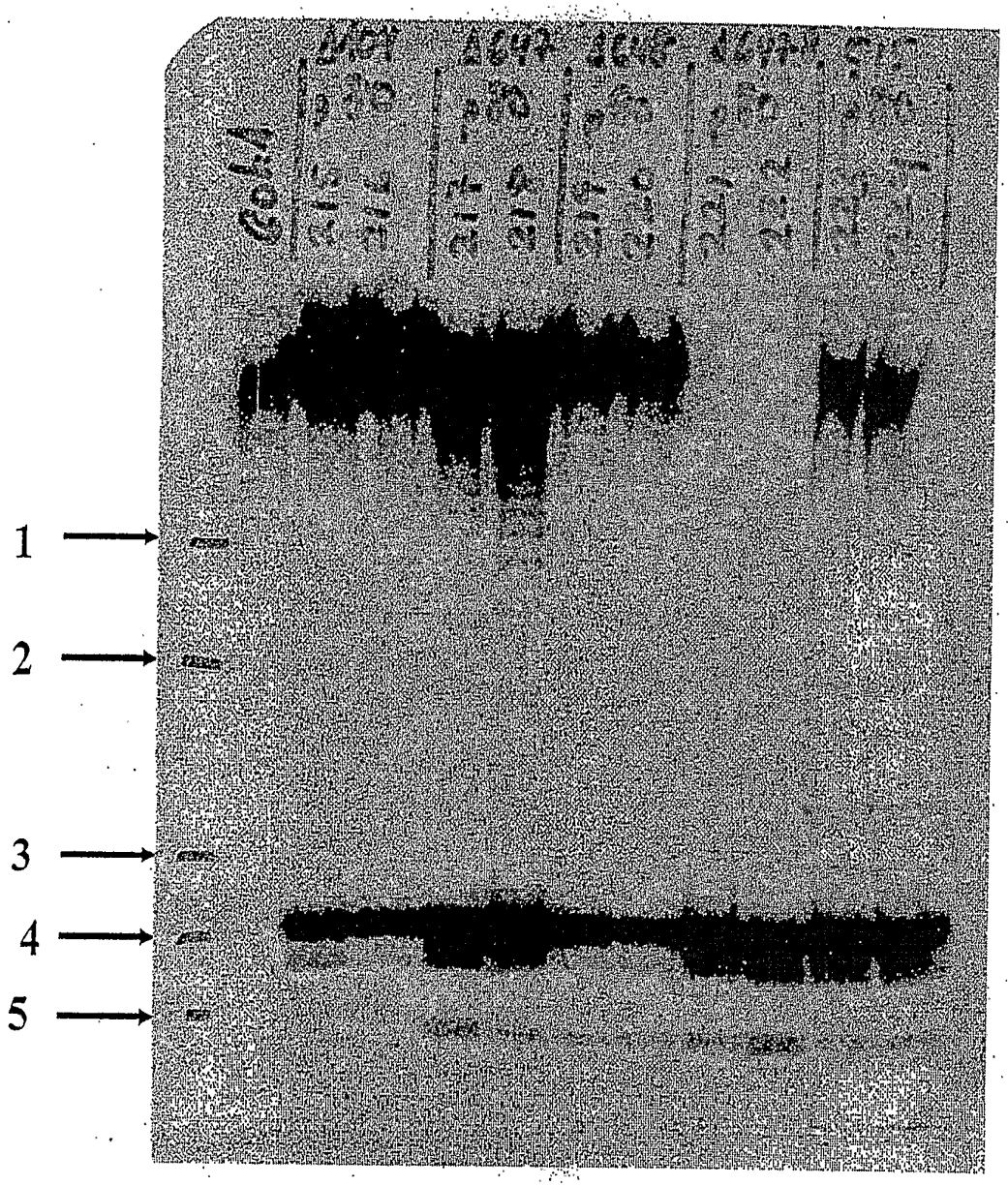
Figure 48: In Coh1, only the gbs80 protein and one sortase (sag0647 *or* sag0648) is required for polymerization



Over expression of gbs80 in various strain backgrounds (two clones each).

Total protein extract preparations.

Only the double sortase mutant does not polymerize gbs80.

Gbs80 is polymerized in the DK515 strain background (lacks adhesin island 1, adhesin island 2 is 2603-like). Presumably, sag1405&sag1406 are responsible for polymerization.

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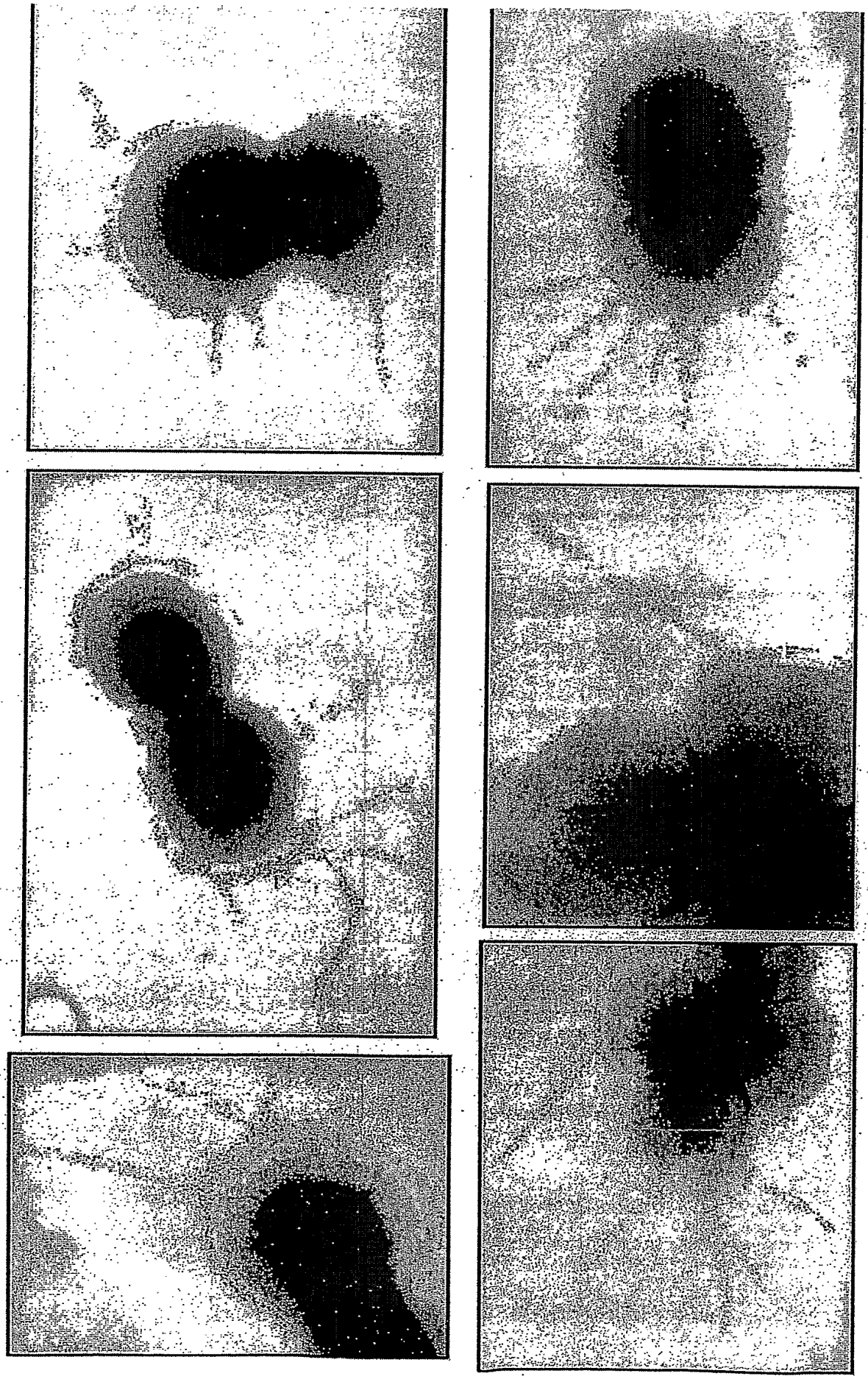

FIGURE 49

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GBS STRAIN JM9030013
IEM anti-GBS104

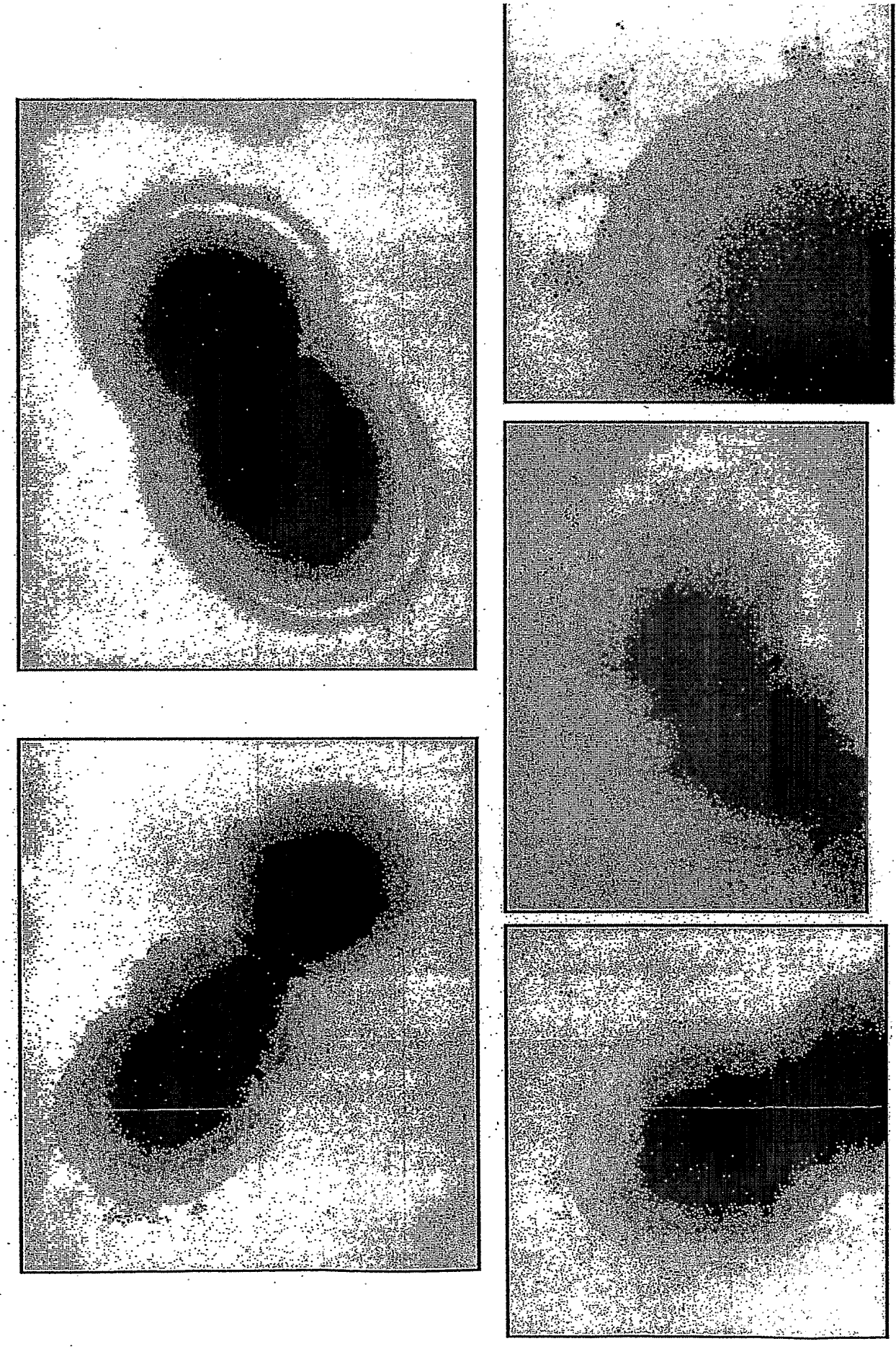


FIGURE 50.

PCT/US05/27239

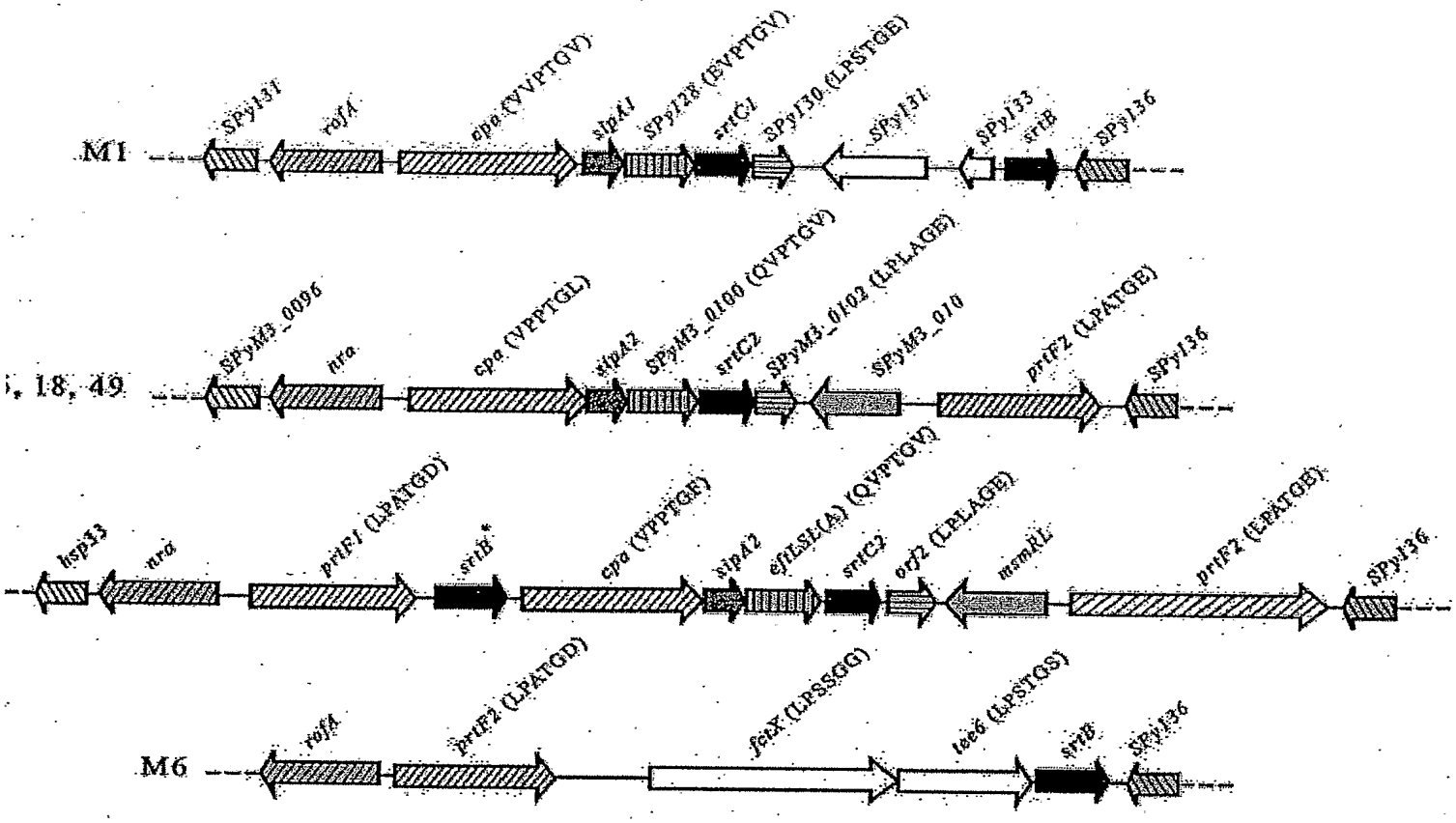


FIGURE 51

PCT/US05/27239

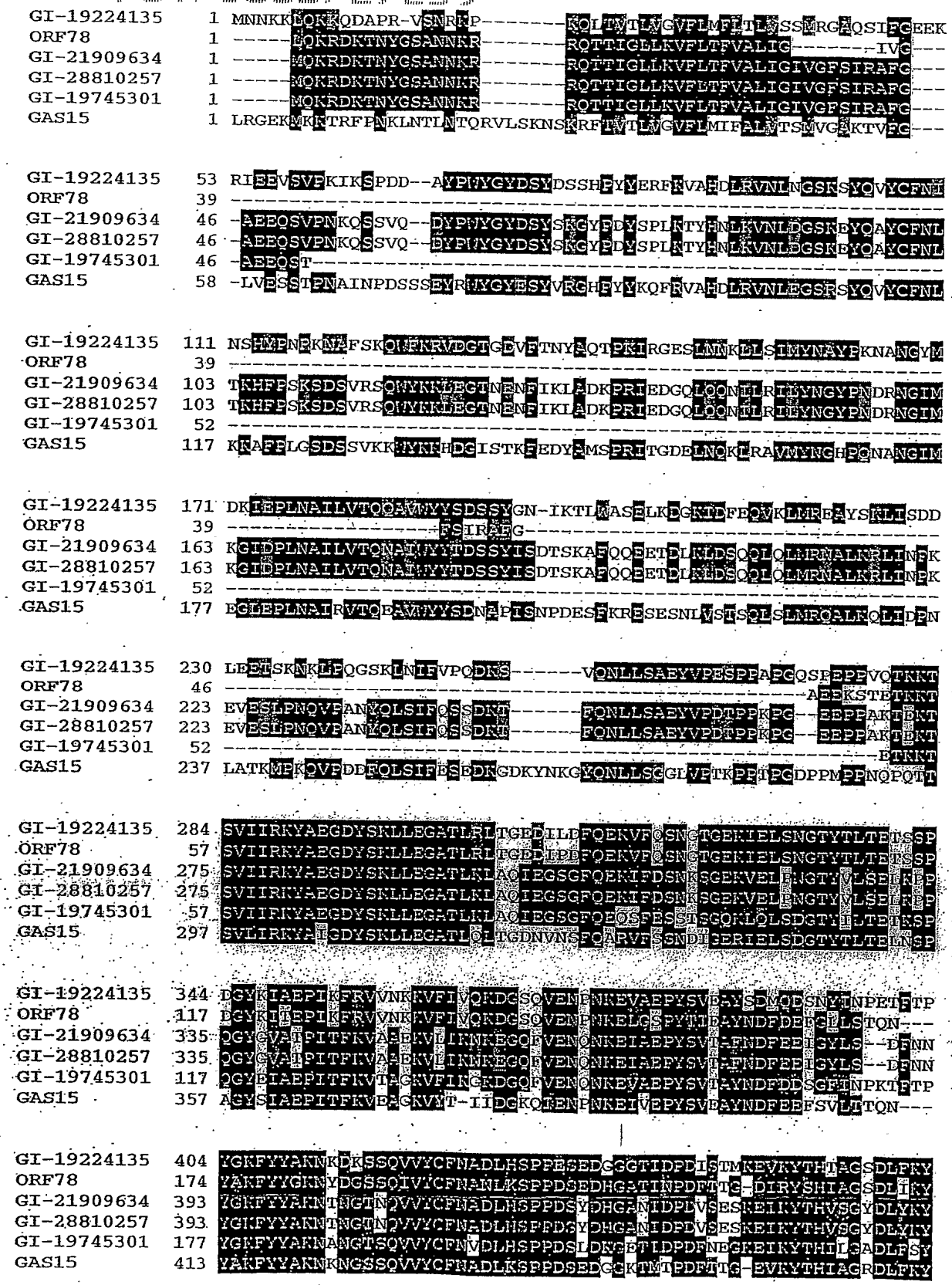


FIGURE 52

PCT/US05/27239

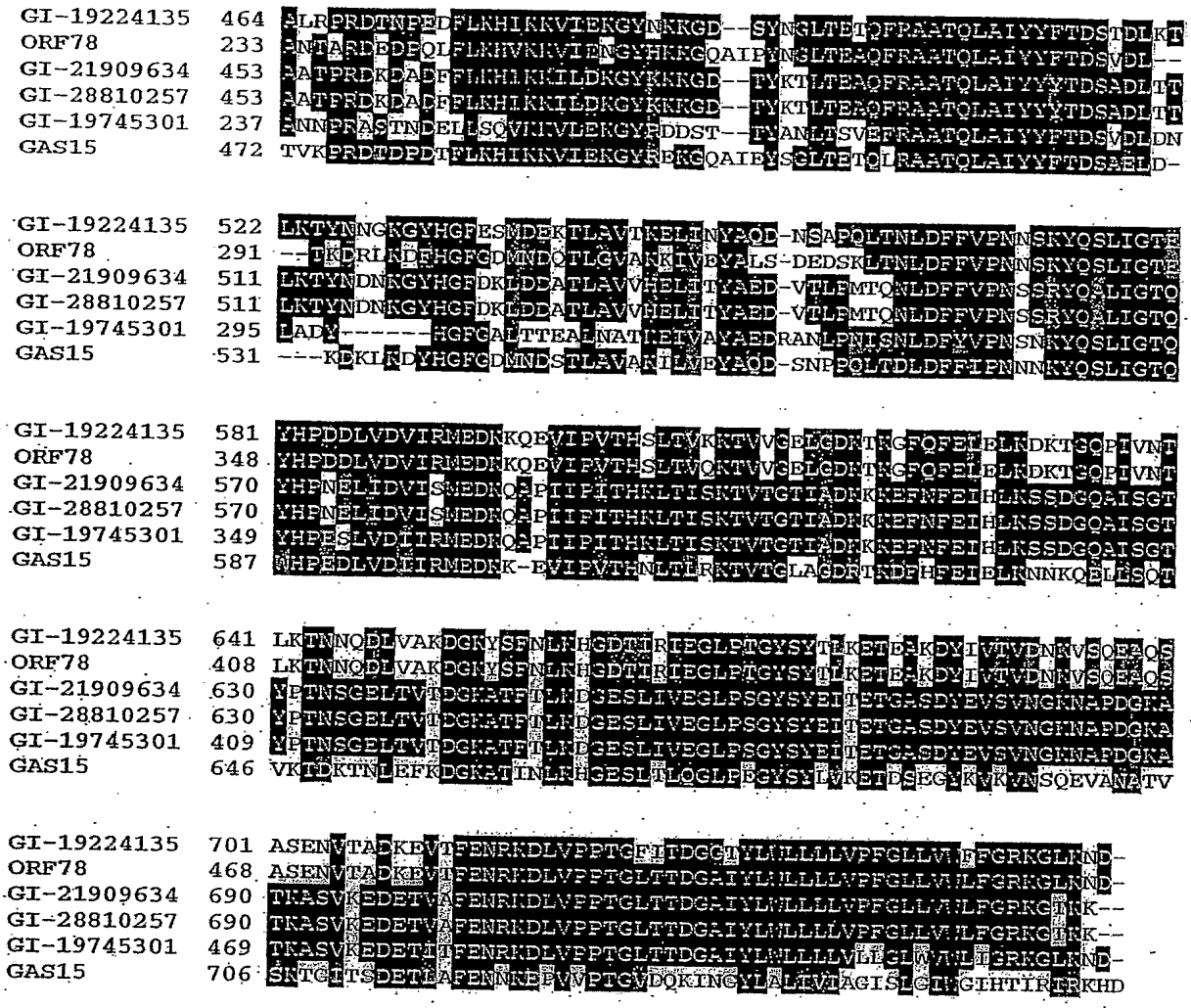


FIGURE 52A

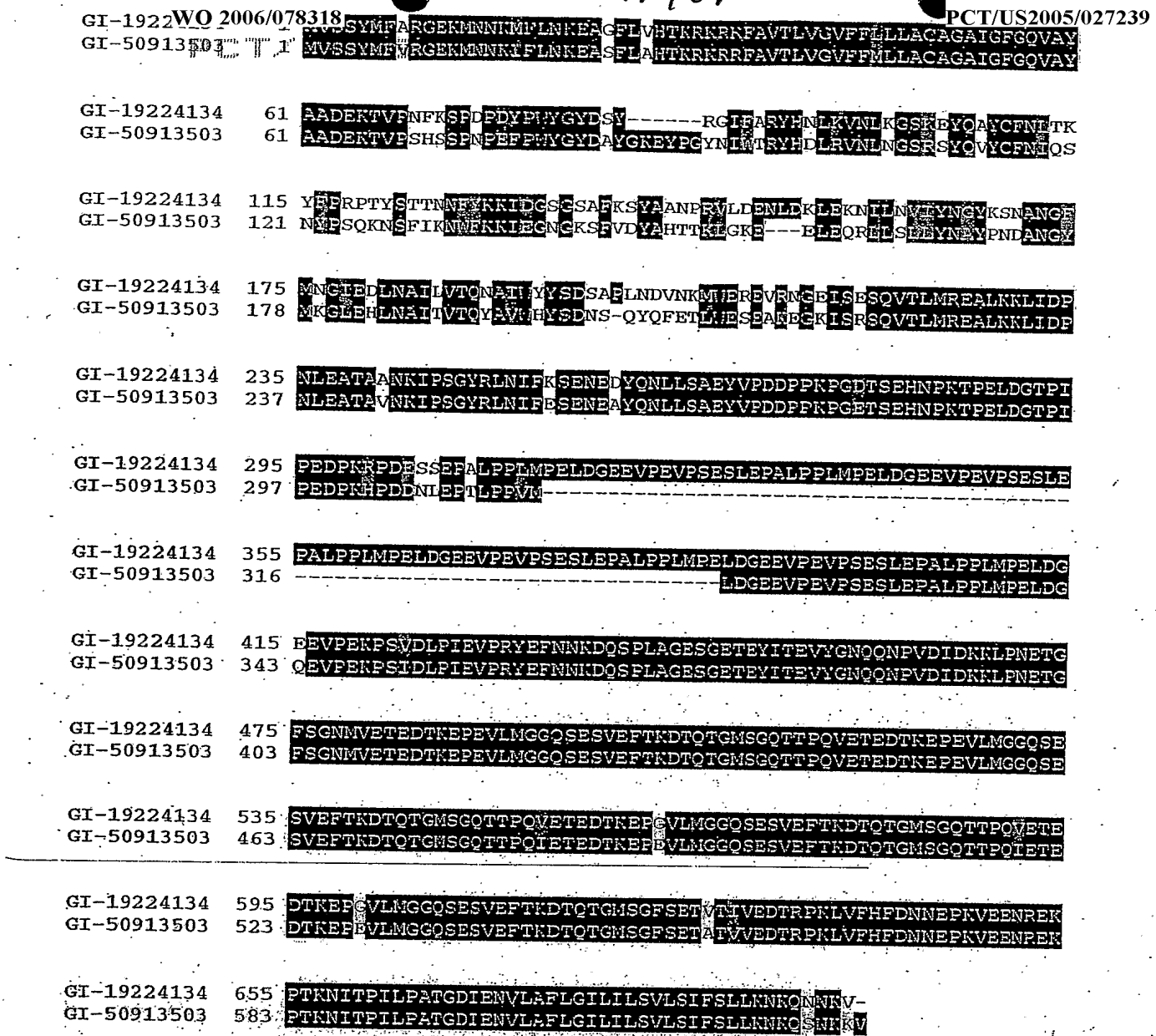
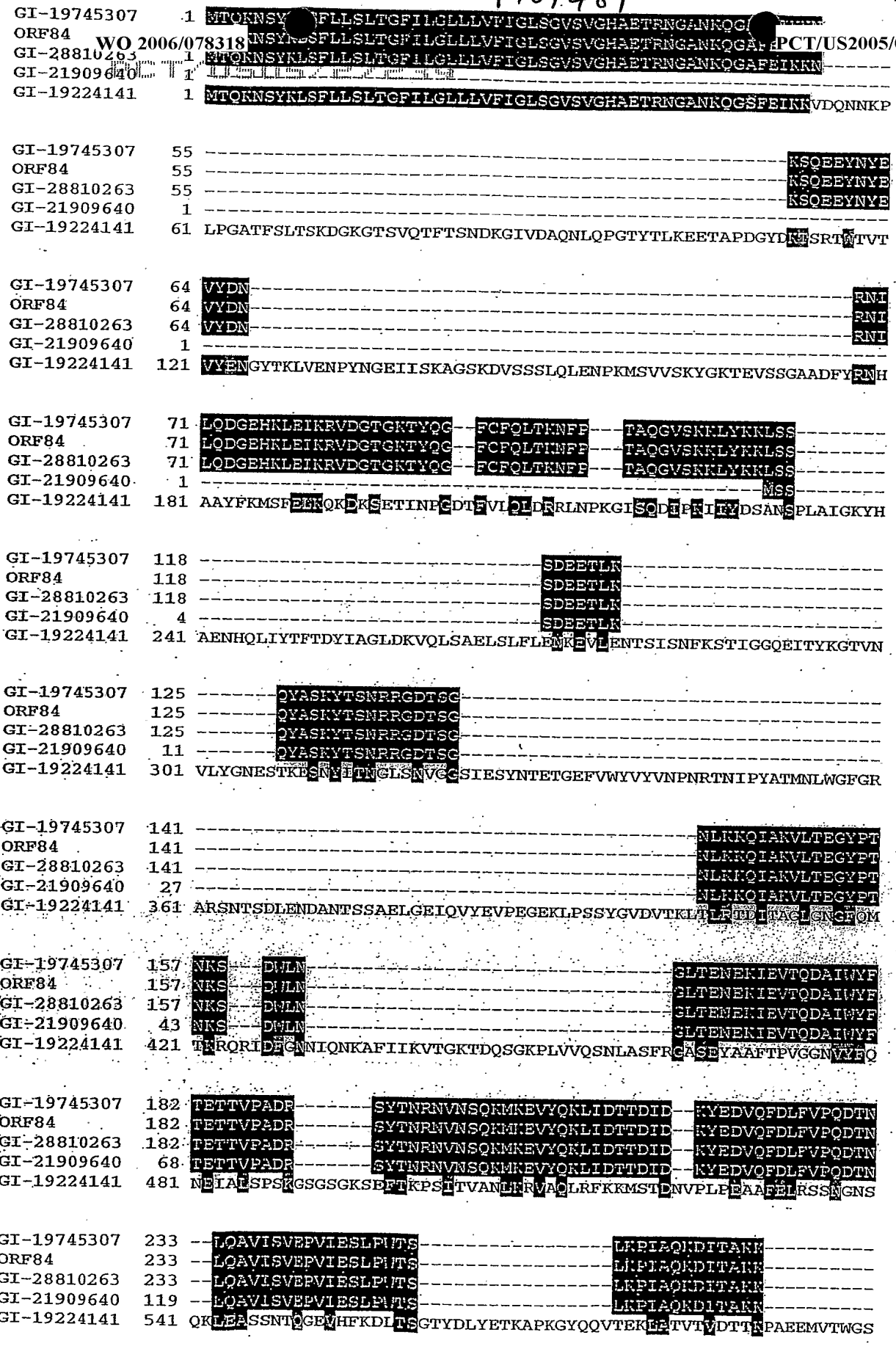


FIGURE 53


GI-19745307 1 MTQKNSY FLLSLTGFILGLLLVFIGLSGVSVGHAETRNGANKQG
ORF84
GI-28810263 1 MTQKNSYKLSFLLSLTGFILGLLLVFIGLSGVSVGHAETRNGANKQGAFEIKKN
GI-21909640 1
GI-19224141 1 MTQKNSYKLSFLLSLTGFILGLLLVFIGLSGVSVGHAETRNGANKQGSFEIKKVDQNNKP
GI-19745307 55
ORF84 55 KSQEEYNYE
GI-28810263 55 KSQEEYNYE
GI-21909640 1 KSQEEYNYE
GI-19224141 61 LPGATFSLTSKDGKGTSVQTFTSNDKGIVDAQNLQPGTYTLKEETAPDGYDKESRTWTVT
GI-19745307 64 VYDN RNI
ORF84 64 VYDN RNI
GI-28810263 64 VYDN RNI
GI-21909640 1
GI-19224141 121 VYENGYTKLVENPYNGEIISKAGSKDVSSSLQLENPKMSVVSKYGKTEVSSGAADFYRNH
GI-19745307 71 LQDGEHKLEIKRVDGTGKTYQG FCFQLTKNFP TAQGVSKKLYKKLSS
ORF84 71 LQDGEHKLEIKRVDGTGKTYQG FCFQLTKNFP TAQGVSKKLYKKLSS
GI-28810263 71 LQDGEHKLEIKRVDGTGKTYQG FCFQLTKNFP TAQGVSKKLYKKLSS
GI-21909640 1 MSS
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GI-19745307 118 SDEETLK
ORF84 118 SDEETLK
GI-28810263 118 SDEETLK
GI-21909640 4 SDEETLK
GI-19224141 241 AENHQLIYTFTDYIAGLDKVQLSAELSLFLENKEVLENTSISNFKSTIGGQEITYKGTVN
GI-19745307 125 QYASKYTSNRRGDTSG
ORF84 125 QYASKYTSNRRGDTSG
GI-28810263 125 QYASKYTSNRRGDTSG
GI-21909640 11 QYASKYTSNRRGDTSG
GI-19224141 301 VLYGNESTKESNYITNGLSNVCGSIESYNTETGEFVWYVYVNPNRTNIPYATMNLWGFGR
GI-19745307 141 NLKKQIAKVLTEGYPT
ORF84 141 NLKKQIAKVLTEGYPT
GI-28810263 141 NLKKQIAKVLTEGYPT
GI-21909640 27 NLKKQIAKVLTEGYPT
GI-19224141 361 ARSNTSDLENDANTSSAELGEIQVYEVPEGEKLPSSYGVDVTKLTLRTDITAGLCNGFQM
GI-19745307 157 NKS DVLN GLTENEKIEVTQDAIWYF
ORF84 157 NKS DVLN GLTENEKIEVTQDAIWYF
GI-28810263 157 NKS DVLN GLTENEKIEVTQDAIWYF
GI-21909640 43 NKS DVLN GLTENEKIEVTQDAIWYF
GI-19224141 421 TKRQRIDFGNNIQNKAFIIKVTGKTDQSGKPLVVQSNLASFRGASEYAAFTPVGGNVYFQ
GI-19745307 182 TETTVPADR SYTNRNVNSQKMKEVYQKLIDTTDID KYEDVQFDLFVPQDTN
ORF84 182 TETTVPADR SYTNRNVNSQKMKEVYQKLIDTTDID KYEDVQFDLFVPQDTN
GI-28810263 182 TETTVPADR SYTNRNVNSQKMKEVYQKLIDTTDID KYEDVQFDLFVPQDTN
GI-21909640 68 TETTVPADR SYTNRNVNSQKMKEVYQKLIDTTDID KYEDVQFDLFVPQDTN
GI-19224141 481 NEIALSPSKGSGSGKSEPTKPSTTVANLRRVAQLRFKKMSTDNVPLPEAAFELRSSNGNS
GI-19745307 233 LQAVISVEPVIESLPITS LKPIAQKDITAKK
ORF84 233 LQAVISVEPVIESLPITS LKPIAQKDITAKK
GI-28810263 233 LQAVISVEPVIESLPITS LKPIAQKDITAKK
GI-21909640 119 LQAVISVEPVIESLPITS LKPIAQKDITAKK
GI-19224141 541 QKLEASSNTQGEVHFKDLTSGTYDLYETKAPKGYQQVTEKEATVTVDTTNPAEEMVTWGS

FIGURE 54